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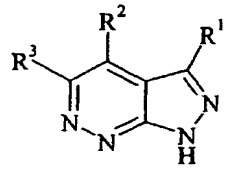
(54) Title: PYRAZOLOPYRIDAZINE DERIVATIVES, PROCESS FOR PREPARATION AND USE FOR THE INHIBITION OF GSK-3



(I)

(57) Abstract: Certain compounds of formula (I) or a salt thereof and/or a solvate thereof, wherein, R^1, R^2 and R^3 are as defined in the specification, processes for the preparation of such compounds, a pharmaceutical composition comprising such compounds and the use of such compounds in medicine.

PYRAZOLOPYRIDAZINE DERIVATIVES, PROCESS FOR PREPARATION AND USE FOR THE INHIBITION OF GSK-3

This invention relates to novel compounds, in particular to novel pyrazolopyridazine derivatives, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds in medicine.

GSK-3 is a serine/threonine protein kinase composed of two isoforms (α and β) which are encoded by distinct genes. GSK-3 is one of several protein kinases which phosphorylates glycogen synthase (GS) (Embi *et al., Eur. J. Biochem.*, **(107)**, 519-527, (1980)). The α and β isoforms have a monomeric structure and are both found in mammalian cells. Both isoforms phosphorylate muscle glycogen synthase (Cross *et al., Biochemical Journal*, **(303)**, 21-26, (1994)) and these two isoforms show good homology between species (*e.g.* human and rabbit GSK-3α are 96% identical).

Type II diabetes (or Non-Insulin Dependent Diabetes Mellitus, NIDDM) is a multifactorial disease. Hyperglycaemia is due to insulin resistance in the liver, muscle and other tissues coupled with inadequate or defective secretion of insulin from pancreatic islets. Skeletal muscle is the major site for insulin-stimulated glucose uptake and in this tissue, glucose removed from the circulation is either metabolised through glycolysis and the TCA cycle, or stored as glycogen. Muscle glycogen deposition plays the more important role in glucose homeostasis and Type II diabetic subjects have defective muscle glycogen storage.

The stimulation of glycogen synthesis by insulin in skeletal muscle results from the dephosphorylation and activation of glycogen synthase (Villar-Palasi C. and Larner J., *Biochim. Biophys. Acta.*, **(39)**, 171-173, (1960), Parker P.J. *et al., Eur. J. Biochem.*, **(130)**, 227-234, (1983) and Cohen P., *Biochem. Soc. Trans.*, **(21)**, 555-567, (1993)). The phosphorylation and dephosphorylation of GS are mediated by specific kinases and phosphatases. GSK-3 is responsible for phosphorylation and deactivation of GS, while glycogen bound protein phosphatase 1 (PP1G) dephosphorylates and activates GS. Insulin both inactivates GSK-3 and activates PP1G (Srivastava A.K. and Pandey S.K., *Mol. and Cellular Biochem.*, **(182)**, 135-141, (1998)).

Chen *et al.* (*Diabetes*, **(43)**, 1234-1241, (1994)) found that there was no difference in the mRNA abundance of PP1G between patients with Type II diabetes and control

patients, suggesting that an increase in GSK-3 activity might be important in Type II diabetes. It has also recently been demonstrated that GSK-3 is overexpressed in Type II diabetic muscle and that an inverse correlation exists between skeletal muscle GSK-3α activity and insulin action (Nikoulina *et al.*, *Diabetes*, **(49)**, 263-271, (2000)). Overexpression of GSK-3β and constitutively active GSK-3β(S9A, S9E) mutants in HEK-293 cells resulted in suppression of glycogen synthase activity (Eldar-Finkelman *et al.*, *PNAS*, **(93)**, 10228-10233, (1996)) and overexpression of GSK-3β in CHO cells, expressing both insulin receptor and insulin receptor substrate 1 (IRS-1), resulted in an impairment of insulin action (Eldar-Finkelman and Krebs, *PNAS*, **(94)**, 9660-9664, (1997)). Recent evidence for the involvement of elevated GSK-3 activity and the development of insulin resistance and type II diabetes in adipose tissue has emerged from studies undertaken in diabetes and obesity prone C57BL/6J mice (Eldar-Finkelman *et al.*, *Diabetes*, **(48)**, 1662-1666, (1999)).

GSK-3 has been shown to phosphorylate other proteins *in vitro* including the eukaryotic initiation factor eIF-2B at $Serine^{540}$ (Welsh *et al.*, *FEBS Letts.*, **(421)**, 125-130, (1998)). This phosphorylation results in an inhibition of eIF-2B activity and leads to a reduction in this key regulatory step of translation. In disease states, such as diabetes, where there is elevated GSK-3 activity this could result in a reduction of translation and potentially contribute to the pathology of the disease.

Several aspects of GSK-3 functions and regulation in addition to modulation of glycogen synthase activity indicate that inhibitors of this enzyme may be effective in treatment of disorders of the central nervous system. GSK-3 activity is subject to inhibitory phosphorylation by PI 3 kinase-mediated or Wnt-1 class-mediated signals that can be mimicked by treatment with lithium, a low mM inhibitor of GSK-3 (Stambolic V., Ruel L. and Woodgett J.R., *Curr. Biol.*, **(6)**, 1664-8, (1996)).

GSK-3 inhibitors may be of value as neuroprotectants in treatment of acute stroke and other neurotraumatic injuries. Roles for PI 3-kinase signalling through PKB/akt to promote neuronal cell survival are well established, and GSK-3 is one of a number of PKB/akt substrates to be identified that can contribute to the inhibition of apoptosis via this pathway (Pap and Cooper, *J. Biol. Chem.*, **(273)**, 19929-19932, ((1998)). Evidence suggests that astrocytic glycogen can provide an alternative energy source to facilitate neuronal survival under conditions of glucose deprivation (for example, see Ransom B.R.

and Fern R., *Glia*, **(21)**, 134-141, (1997) and references therein). Lithium is known to protect cerebellar granule neurons from death (D'Mello *et al.*, *Exp. Cell Res.*, **(211)**, 332-338, (1994) and Volonte *et al.*, *Neurosci. Letts.*, **(172)**, 6-10, (1994)) and chronic lithium treatment has demonstrable efficacy in the middle cerebral artery occlusion model of stroke in rodents (Nonaka and Chuang, *Neuroreport*, **(9)**, 2081-2084, (1998)). Wnt-induced axonal spreading and branching in neuronal culture models has been shown to correlate with GSK-3 inhibition (Lucas and Salinas, *Dev. Biol.*, **(192)**, 31-44, (1997)) suggesting additional value of GSK-3 inhibitors in promoting neuronal regeneration following neurotraumatic insult.

Tau and β-catenin, two known *in vivo* substrates of GSK-3, are of direct relevance in consideration of further aspects of the value of GSK-3 inhibitors in relation to treatment of chronic neurodegenerative conditions. Tau hyperphosphorylation is an early event in neurodegenerative conditions such as Alzheimer's disease (AD), and is postulated to promote microtubule disassembly. Lithium has been reported to reduce the phosphorylation of tau, enhance the binding of tau to microtubules, and promote microtubule assembly through direct and reversible inhibition of glycogen synthase kinase-3 (Hong M., Chen D.C., Klein P.S. and Lee V.M., *J. Biol. Chem.*, **(272)**, 25326-32, (1997). β-catenin is phosphorylated by GSK-3 as part of a tripartite complex with axin, resulting in β-catenin being targetted for degradation (Ikeda *et al.*, *J. EMBO.*, **(17)**, 1371-1384, (1998)). Inhibition of GSK-3 activity is a key mechanism by which cytosolic levels of catenin are stabilised and hence promote β-catenin-LEF-1/TCF transcriptional activity (Eastman, Grosschedl, *Curr. Opin. Cell. Biol.*, **(11)**, 233, (1999)). Rapid onset AD mutations in presenilin-1 (PS-1) have been shown to decrease the cytosolic β-catenin pool in transgenic mice. Further evidence suggests that such a reduction in available β-catenin may increase neuronal sensitivity to amyloid mediated death through inhibition of β-catenin-LEF-1/TCF transcriptional regulation of neuroprotective genes (Zhang *et al.*, *Nature*, **(395)**, 698-702, (1998)). A likely mechanism is suggested by the finding that mutant PS-1 protein confers decreased inactivation of GSK-3 compared with normal PS-1 (Weihl C.C., Ghadge G.D., Kennedy S.G., Hay N., Miller R.J. and Roos R.P., *J. Neurosci.*, **(19)**, 5360-5369, (1999)).

International Patent Application Publication Number WO 97/41854 (University of Pennsylvania) discloses that an effective drug for the treatment of manic depression is lithium, but that there are serious drawbacks associated with this treatment. Whilst the precise mechanism of action of this drug for treatment of manic depression remains to be fully defined, current models suggest that inhibition of GSK-3 is a relevant target that contributes to the modulation of AP-1 DNA binding activity observed with this compound (see Manji *et al.*, *J. Clin. Psychiatry*, **(60)** (suppl 2), 27-39, (1999) for review).

GSK-3 inhibitors may also be of value in treatment of schizophrenia. Reduced levels of β-catenin have been reported in schizophrenic patients (Cotter D., Kerwin R., al-Sarraji S., Brion J.P., Chadwich A., Lovestone S., Anderton B., and Everall I., *Neuroreport*, **(9)**, 1379-1383, (1998)) and defects in pre-pulse inhibition to startle response have been observed in schizophrenic patients (Swerdlow *et al.*, *Arch. Gen. Psychiat.*, **(51)**, 139-154, (1994)). Mice lacking the adaptor protein dishevelled-1, an essential mediator of Wnt-induced inhibition of GSK-3, exhibit both a behavioural disorder and defects in pre-pulse inhibition to startle response (Lijam N., Paylor R., McDonald M.P., Crawley J.N., Deng C.X., Herrup K., Stevens K.E., Maccaferri G., McBain C.J., Sussman D.J., and Wynshaw-Boris A., *Cell*, **(90)**, 895-905, (1997)). Together, these findings implicate deregulation of GSK-3 activity as contributing to schizophrenia. Hence, small molecule inhibitors of GSK-3 catalytic activity may be effective in treatment of this mood disorder.

The finding that transient β-catenin stabilisation may play a role in hair development (Gat *et al.*, *Cell*, **(95)**, 605-614, (1998)) suggests that GSK-3 inhibitors could be used in the treatment of baldness.

Studies on fibroblasts from the GSK-3β knockout mouse (Hoeflich K.P. *et al.*, *Nature*, **(406)**, 86-90, (2000)) support a role for this kinase in positively regulating the activity of NFkB. This transcription factor mediates cellular responses to a number of inflammatory stimuli. Therefore, pharmacologic inhibition of GSK-3 may be of use in treating inflammatory disorders through the negative regulation of NFkB activity.

The compounds of the present invention are pyrazolopyridazine derivatives. Other pyrazolopyridazine derivatives have been described previously for use in alternative medicinal applications. For example, International Patent Application, Publication Number WO 00/26211 describes a series of heterocyclic compounds, which may include

pyrazolopyridazines, that exhibit biological activity as inhibitors of thrombin. WO 98/43962 describes various fused heterocyclic compounds, which may include pyrazolopyridazines, which are useful as antagonists of the $\alpha_V\beta_3$-integrin and related cell surface adhesive protein receptors. Such compounds are indicated to be useful in the treatment of conditions such as angiogenic disorders, inflammation, bone degradation, cancer metastasis, diabetic retinopathy, thrombosis, restenosis, macular degeneration, and other conditions mediated by cell adhesion and/or cell migration and/or angiogenesis.

Co-pending International Patent Application, Publication Number WO 02/088078 describes a series of 3-aminopyrazolo[3,4-c]pyridazines as GSK-3 inhibitors.

Pyrazolo[3,4-c]pyridazines have also been disclosed in the following journal articles:

Fawzy M.M. *et al.*, *Asian. J. Chem.*, **4(3)**, 500-507, (1992);

Caronna S. *et al.*, *Boll. Chim. Farm.*, **125(4)**, 114, (1986);

Deeb A. *et al.*, *Heterocycles*, **32(5)**, 895, (1991);

Ismail M.F., *Phosphorus, Sulfur Silicon Relat. Elem.*, **142**, 93-99, (1998);

Ismail M.F., *Synth. Commun.*, **28(19)**, 3609-3618, (1998);

Shalaby A.A. *et al.*, *J. Chin. Chem. Soc (Tapei)*, **41(4)**, 477-480, (1994);

Ismail, M.F., *Collect. Czech. Chem. Commun.*, **57(10)**, 2199-2202, (1992); and

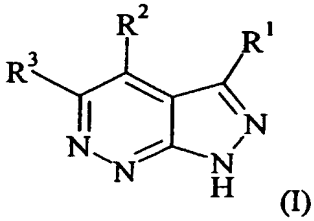
Eichorn T.A. et al., *Helv. Chim. Acta.*, **71(5)**, 988-991, (1988).

It is noted that none of the compounds described in the above-mentioned references have been shown to exhibit biological activity as inhibitors of GSK-3.

We have now discovered that a series of pyrazolo[3,4-c]pyridazines are potent and selective inhibitors of GSK-3. These compounds are indicated to be useful for the treatment and/or prophylaxis of conditions associated with a need for inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke,

cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

Accordingly, in a first aspect, the present invention provides a compound of formula (I) or a salt thereof and/or a solvate thereof,



(I)

wherein,

R^1 is H, halo, alkyl, hydroxyalkyl, aryl wherein the aryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, $-CF_3$, -OH, $-OCF_3$, $-NO_2$, alkyl, alkenyl, alkynyl, alkoxy and dialkylamino; arylalkoxyalkyl, $-NHR^4$, $-NH(CH_2)_nR^5$, $-N=CHR^6$ or heteroaryl wherein the heteroaryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, $-CF_3$, -OH, =O, $-OCF_3$, $-NO_2$, alkyl, alkenyl, alkynyl, alkoxy and di-alkylamino;

R^2 is H, alkyl or aryl wherein the aryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, $-CF_3$, -OH, $-OCF_3$, $-NO_2$, alkyl, alkenyl, alkynyl, alkoxy and dialkylamino;

R^3 is halo, aryl wherein the aryl group may be optionally substituted with one or more groups, which may be the same or different, selected from halo, -CN, $-CF_3$, -OH, $-OCF_3$, $-NO_2$, alkyl, alkenyl, alkynyl, alkoxy, dialkylamino; or heteroaryl wherein the heteroaryl group may be optionally substituted with one or more groups, which may be the same or

different, selected from halo, -CN, -CF_3, -OH, –OCF_3, -NO_2, alkyl, alkenyl, alkynyl, alkoxy, dialkylamino;

R^4 is alkyl, heteroaryl wherein the heteroaryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, -CF_3, -OH, –OCF_3, -NO_2, alkyl, alkenyl, alkynyl, alkoxy and dialkylamino; cycloC_{3-8} alkyl wherein the cycloalkyl group may be optionally substituted with one or more substituents, which may be the same or different, selected from alkyl, aryl and –CO_2R^7, or, said cycloalkyl group is fused with an aryl ring to form a bicyclic moiety; or heterocyclyl wherein the heterocyclyl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, -CF_3, -OH, –OCF_3, -NO_2, alkyl, alkenyl, alkynyl, alkoxy and dialkylamino;

R^5 is cycloC_{3-8} alkyl, aryloxy, aryl wherein the aryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, -CF_3, -OH, –OCF_3, -NO_2, alkyl, alkenyl, alkynyl, alkoxy, dialkylamino; or heteroaryl wherein the heteroaryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, -CF_3, -OH, –OCF_3, -NO_2, alkyl, alkenyl, alkynyl, alkoxy, dialkylamino;

R^6 is aryl;

R^7 is alkyl; and

n is 1, 2, 3, 4, 5 or 6;

with the proviso that said compound of formula (I) is not selected from the following compounds:

4,5-Diphenyl-3-methyl-1H-pyrazolo[3,4-c]pyridazine;

3, 4,5-Diphenyl-3-methyl-1H-pyrazolo[3,4-c]pyridazine;

3,4,5-Triphenyl-3-methyl-1H-pyrazolo[3,4-c]pyridazine;

3-(4-Methoxyphenyl)-5-(4-methylphenyl)-1H-pyrazolo[3,4-c]pyridazine;

3-Phenyl-5-(4-methylphenyl)-1H-pyrazolo[3,4-c]pyridazine;
3-(3-Chlorophenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;
3-(3-Bromophenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Bromophenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Chlorophenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Methoxyphenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;
3,5-Diphenyl-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Methoxyphenyl)-5-chloro-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Fluorophenyl)-5-chloro-1H-pyrazolo[3,4-c]pyridazine;
3-(2,5-Dichlorophenyl)-5-chloro-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Methylphenyl)-5-chloro-1H-pyrazolo[3,4-c]pyridazine; and
3-Phenyl-5-chloro-1H-pyrazolo[3,4-c]pyridazine;

Suitably, R^1 is H, halo, alkyl, hydroxyalkyl, aryl wherein the aryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, $-CF_3$, -OH, $-OCF_3$, $-NO_2$, alkyl, alkenyl, alkynyl, alkoxy and dialkylamino; arylalkoxyalkyl, $-NH(CH_2)_nR^5$, where R^5 is cycloC_{3-8} alkyl or aryloxy; $-N=CHR^6$ or heteroaryl wherein the heteroaryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, $-CF_3$, -OH, =O, $-OCF_3$, $-NO_2$, alkyl, alkenyl, alkynyl, alkoxy and di-alkylamino. Suitably, R^1 is H, halo, alkyl, hydroxyalkyl, aryl, arylalkoxyalkyl, $-NHR^4$, $-NH(CH_2)_nR^5$, $-N=CHR^6$, or heteroaryl wherein the heteroaryl group is substituted by alkoxy or =O. Preferably, R^1 is H, methyl, phenyl, -N=CHPh, bromo, 3-(2-MeO-pyridyl), 3-(2-pyridone), $-CH_2OCH_2Ph$, $-CH_2OH$, $-NH(CH_2)_4$(4-Et-Piperazinyl-1-yl), $-NHCH_2Ph$, $-NH(CH_2)_3Ph$, -NH(3-pyridyl), $-NHCH_2$cyclo-pentyl, $-NHCH_2$cyclo-propyl, $-NH(CH_2)_2Ph$, -NHPr, $-NHCH_2$-(2-Cl-Ph), $-NHCH_2$-(3-Cl-Ph), $-NHCH_2$-(4-Cl-Ph), $-NHCH_2$-(3-Br-Ph), $-NHCH_2$-(2-F-Ph), $-NHCH_2$-(3-F-Ph), $-NH(CH_2)_2OPh$, $-NH(CH_2)_5CH_3$, -NHcyclo-pentyl, -NHcyclo-hexyl, -NHcyclo-heptyl, $-NHCH_2$-(3-pyridyl), -NH-4-tetrahydrothiapyranyl, -NH-4-(cyclo-hexyl-CO_2Et), -NH-(4-methyl-cyclo-hexyl), -NH-(4-phenyl-cyclo-hexyl), -NH-*iso*-butyl, -NH-*iso*-propyl, -NH-(2,2-dimethylpropyl), -NH-4-(1-propyl-piperidyl), -NH-4-(1-methyl-piperidyl), -NH-4-tetrahydropyranyl, $-NHCH_2$-(4-MeO-Ph), $-NHCH_2$-(4-Br-Ph), -NH-(2-indanyl),or -

$NHCH_2$(4-(4-Me-piperazin-1-yl)-Ph). More preferably, R^1 is H, methyl, phenyl, -N=CHPh, bromo, 3-(2-MeO-pyridyl), 3-(2-pyridone), $-CH_2OCH_2Ph$, $-CH_2OH$, $-NHCH_2$cyclo-pentyl, $-NHCH_2$cyclo-propyl or $-NH(CH_2)_2OPh$.

Suitably, R^2 is H, alkyl or aryl. Preferably, R^2 is H, methyl or phenyl.

Suitably, R^3 is halo, phenyl wherein the phenyl group may be optionally substituted by one or more groups, which may be the same or different, selected from halo and alkyl; or heteroaryl. Preferably, R^3 is chloro, phenyl, 3-methylphenyl, 2-chlorophenyl, 2,3-di-fluorophenyl or 3-pyridyl.

Suitably, R^4 is alkyl, heteroaryl, cycloC_{3-8} alkyl wherein the cycloalkyl group may be optionally substituted by one or more substituents, which may be the same or different, selected from alkyl, aryl and $-CO_2R^7$, or, said cycloalkyl group is fused with an aryl ring to form a bicyclic moiety; or heterocyclyl wherein the heterocyclyl group may be optionally substituted by alkyl.

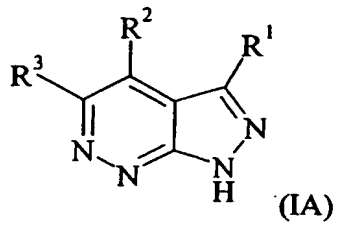
Suitably, R^5 is cycloC_{3-8} alkyl, aryloxy, aryl wherein the aryl group may be optionally substituted by one or more substituents, which may be the same or different, selected from halo and alkoxy; or heteroaryl;

Suitably R^6 is aryl, for example phenyl.

Suitably R^7 is alkyl, for example ethyl.

Suitably, n is 1, 2, 3 or 4.

In a preferred aspect of the present invention there is provided a subset of compounds of formula (I), of formula (IA),



(IA)

or a salt thereof, or a solvate thereof, wherein,

R^1 is H, halo, alkyl, hydroxyalkyl, aryl; arylalkoxyalkyl, $-NHR^4$, $-NH(CH_2)_nR^5$, $-N=CHR^6$ or heteroaryl wherein the heteroaryl group may be optionally substituted by alkoxy or =O;

R^2 is H, alkyl or aryl;

R^3 is halo, aryl wherein the aryl group may be optionally substituted by one or more groups, which may be the same or different, selected from halo and alkyl; or heteroaryl;

R^4 is alkyl, heteroaryl, cycloC_{3-8} alkyl wherein the cycloalkyl group may be optionally substituted by one or more substituents, which may be the same or different, selected from alkyl, aryl and $-CO_2R^7$, or, said cycloalkyl group is fused with an aryl ring to form a bicyclic moiety; or heterocyclyl wherein the heterocyclyl group may be optionally substituted by alkyl;

R^5 is cycloC_{3-8} alkyl, aryloxy, aryl wherein the aryl group may be optionally substituted by one or more substituents, which may be the same or different, selected from halo, alkoxy and heteroaryl wherein the heteroaryl may be optionally substituted by alkyl;

R^6 is aryl;

R^7 is alkyl; and

n is 1, 2, 3 or 4;

with the proviso that said compound of formula (IA) is not selected from the following compounds:

4,5-Diphenyl-3-methyl-1H-pyrazolo[3,4-c]pyridazine;

3,4,5-Triphenyl-3-methyl-1H-pyrazolo[3,4-c]pyridazine;

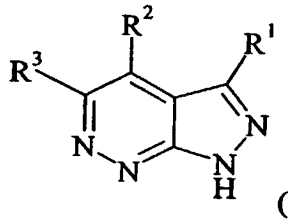
3-Phenyl-5-(4-methylphenyl)-1H-pyrazolo[3,4-c]pyridazine;

3,5-Diphenyl-1H-pyrazolo[3,4-c]pyridazine; and

3-Phenyl-5-chloro-1H-pyrazolo[3,4-c]pyridazine.

Suitably, R^1 is H, halo, alkyl, hydroxyalkyl, aryl; arylalkoxyalkyl, $-NH(CH_2)_nR^5$ where R^5 is cycloC_{3-8} alkyl, aryloxy, $-N=CHR^6$ or heteroaryl wherein the heteroaryl group may be optionally substituted by alkoxy or =O.

In a further preferred aspect of the present invention, there is also provided a subset of compounds of formula (I), of formula (IB) or a salt thereof, or a solvate thereof,



(IB)

wherein,

R^1 is H, methyl, phenyl, -N=CHPh, bromo, 3-(2-MeO-pyridyl), 3-(2-pyridone), $-CH_2OCH_2Ph$, $-CH_2OH$, $-NH(CH_2)_4$(4-Et-Piperazinyl-1-yl), $-NHCH_2Ph$, $-NH(CH_2)_3Ph$, -NH(3-pyridyl), $-NHCH_2$cyclo-pentyl, $-NHCH_2$cyclo-propyl, $-NH(CH_2)_2Ph$, -NHPr, $-NHCH_2$-(2-Cl-Ph), $-NHCH_2$-(3-Cl-Ph), $-NHCH_2$-(4-Cl-Ph), $-NHCH_2$-(3-Br-Ph), $-NHCH_2$-(2-F-Ph), $-NHCH_2$-(3-F-Ph), $-NH(CH_2)_2OPh$, $-NH(CH_2)_5CH_3$, -NHcyclo-pentyl, -NHcyclo-hexyl, -NHcyclo-heptyl, $-NHCH_2$-(3-

pyridyl), -NH-4-tetrahydrothiapyranyl, -NH-4-(cyclo-hexyl-CO_2Et), -NH-(4-methyl-cyclo-hexyl), -NH-(4-phenyl-cyclo-hexyl), -NH-*iso*-butyl, -NH-*iso*-propyl, -NH-(2,2-dimethylpropyl), -NH-4-(1-propyl-piperidyl), -NH-4-(1-methyl-piperidyl), -NH-4-tetrahydropyranyl, -$NHCH_2$-(4-MeO-Ph), -$NHCH_2$-(4-Br-Ph), -NH-(2-indanyl), or -$NHCH_2$(4-(4-Me-piperazin-1-yl)-Ph).

R^2 is H, methyl, or phenyl.

R^3 is chloro, phenyl, 3-methylphenyl, 2-chlorophenyl, 2,3-di-fluorophenyl or 3-pyridyl;

with the proviso that said compound of formula (IB) is not selected from the following compounds:
3,5-Diphenyl-1H-pyrazolo[3,4-c]pyridazine; and
3-Phenyl-5-chloro-1H-pyrazolo[3,4-c]pyridazine.

Suitably, R^1 is H, methyl, phenyl, -N=CHPh, bromo, 3-(2-MeO-pyridyl), 3-(2-pyridone), -CH_2OCH_2Ph, -CH_2OH, -$NHCH_2$cyclo-pentyl or -$NHCH_2$cyclo-propyl.

Preferred compounds of formula (I) which are of special interest as agents useful in the treatment and/or prophylaxis of conditions associated with a need for inhibition of GSK-3 are provided in Table 1 below.

The present invention further provides a compound selected from the list consisting of:
3, 4,5-Diphenyl-3-methyl-1H-pyrazolo[3,4-c]pyridazine;
3,4,5-Triphenyl-3-methyl-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Methoxyphenyl)-5-(4-methylphenyl)-1H-pyrazolo[3,4-c]pyridazine;
3-Phenyl-5-(4-methylphenyl)-1H-pyrazolo[3,4-c]pyridazine;
3-(3-Chlorophenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;
3-(3-Bromophenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Bromophenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Chlorophenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;

3-(4-Methoxyphenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;
3,5-Diphenyl-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Methoxyphenyl)-5-chloro-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Fluorophenyl)-5-chloro-1H-pyrazolo[3,4-c]pyridazine;
3-(2,5-Dichlorophenyl)-5-chloro-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Methylphenyl)-5-chloro-1H-pyrazolo[3,4-c]pyridazine; and
3-Phenyl-5-chloro-1H-pyrazolo[3,4-c]pyridazine;
for use as an inhibitor of glycogen synthase kinase-3.

Certain compounds of formula (I) may contain chiral atoms and/or multiple bonds, and hence may exist in one or more stereoisomeric forms. The present invention encompasses all of the isomeric forms of the compounds of formula (I) whether as individual isomers or as mixtures of isomers, including geometric isomers and racemic modifications.

As used herein the term "alkyl" as a group or part of a group refers to a straight or branched chain saturated aliphatic hydrocarbon radical containing 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms. Such alkyl groups in particular include methyl ("Me"), ethyl ("Et"), n-propyl, *iso*-propyl, n-butyl, *sec*-butyl, *tert*-butyl, pentyl and hexyl. Where appropriate, such alkyl groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino.

As used herein the term "alkenyl" as a group or part of a group refers to a straight or branched chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing 2 to 12 carbon atoms, suitably 2 to 6 carbon atoms. References to "alkenyl" groups include groups which may be in the E- or Z-form or mixtures thereof. Such alkenyl groups in particular include ethenyl, propenyl, butenyl, pentenyl and hexenyl. Where appropriate, such alkenyl groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-6} alkyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino.

As used herein the term "alkynyl" refers to hydrocarbon groups of either straight or branched configuration with one or more carbon-carbon triple bonds which may occur at any stable point in the chain, containing 3 to 12 carbon atoms, suitably 3 to 6 carbon atoms. Such alkynyl groups in particular include propynyl, butynyl and pentynyl. Where

appropriate, such alkynyl groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, -CF_3, -OH, –OCF_3, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino.

As used herein, the term "alkoxy" as a group or part of a group refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Such alkoxy groups in particular include methoxy, ethoxy, n-propoxy, *iso*-propoxy, n-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy. Where appropriate, such alkoxy groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, -CF_3, -OH, –OCF_3, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, aryl and di-C_{1-6} alkylamino.

As used herein, the term "aryl" as a group or part of a group refers to a carbocyclic aromatic radical. Suitably such aryl groups are 5-6 membered monocyclic groups or 8-10 membered fused bicyclic groups, especially phenyl, biphenyl and naphthyl, particularly phenyl. Such aryl groups may be optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, -CF_3, -OH, –OCF_3, -NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy and di-C_{1-6} alkylamino.

As used herein, the term "heteroaryl" as a group or part of a group refers to stable heterocyclic aromatic single and fused rings containing one or more hetero atoms independently selected from nitrogen, oxygen and sulfur. A fused heteroaryl ring system may include carbocyclic rings and need include only one heteroaryl ring. Such heteroaryl groups include furyl, thienyl, pyridazinyl, pyridyl, quinolinyl, indolyl, benzoxazolyl, and benzothiazolyl. Each ring may be optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, -CF_3, -OH, -NO_2, –OCF_3, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino.

As used herein, the terms "heterocyclyl" and "heterocyclic" as a group or part of a group refer to stable heterocyclic non-aromatic single and fused rings containing one or more hetero atoms independently selected from nitrogen, oxygen and sulfur. A fused heterocyclyl ring system may include carbocyclic rings and need include only one heterocyclic ring. Such heterocyclyl groups include piperazinyl, pyrrolidinyl, piperidinyl and morpholinyl. Each ring may be optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -

CN, $-CF_3$, -OH, $-NO_2$, $-OCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl, heteroaryl, arylC_{1-6} alkyl and di-C_{1-6} alkylamino.

As used herein the terms "halo" include iodo, bromo, chloro or fluoro, suitably bromo, chloro and fluoro, especially bromo and chloro.

Composite terms such as "alkoxyalkyl" and "arylalkyl" refer to substituents comprising two interlinked groups, with the group named latterly in the term being the linking group, so that "alkoxyalkyl" means -(alkyl)-(alkoxy) whilst "arylalkyl" means -(alkyl)-(aryl).

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, *inter alia*, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Suitable salts are pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts include the acid addition salts with the conventional pharmaceutical acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

Suitable pharmaceutically acceptable salts include salts of acidic moieties of the compounds of formula (I) when they are present, for example salts of carboxy groups or phenolic hydroxy groups.

Suitable salts of acidic moieties include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine,

cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable solvates are pharmaceutically acceptable solvates.

Suitable pharmaceutically acceptable solvates include hydrates.

For the avoidance of doubt when used herein the term "diabetes" includes diabetes mellitus, especially Type 2 diabetes, and conditions associated with diabetes mellitus.

The term "conditions associated with diabetes" includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

The term "conditions associated with the pre-diabetic state" includes conditions such as insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

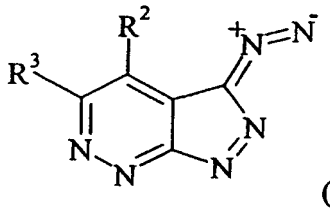
The term "conditions associated with diabetes mellitus itself" includes hyperglycaemia, insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance.

The term "complications associated with diabetes mellitus" includes renal disease, especially renal disease associated with Type II diabetes, neuropathy and retinopathy. Renal diseases associated with Type II diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

The term "neurotraumatic diseases" includes both open or penetrating head trauma, such as caused by surgery, or a closed head trauma injury, such as caused by an injury to the head region, ischaemic stroke including acute stroke, particularly to the brain area, transient ischaemic attacks following coronary by-pass and cognitive decline following other transient ischaemic conditions.

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) where R^1 is H and wherein R^2 and R^3

are as hereinbefore defined in relation to formula (I), or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II),



(II)

wherein R^2 and R^3 are as defined in relation to formula (I), with a suitable protic solvent and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

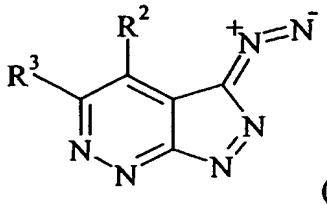
(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed.

The reaction between the compound of formula (II) and a protic solvent is carried out under conventional conditions, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable protic solvents include alcohols, such as methanol. Suitable reaction temperatures include those in the range of 20°C to 150°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 0.5 to 24 hours, preferably 0.5 to 2 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, the compound of formula (II) is heated under reflux in methanol for 0.5 to 2 hours, preferably 1 hour. The resulting reaction mixture is then allowed to cool to ambient temperature and evaporated to dryness to afford the desired compound of formula (I).

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) where R^1 is halo and wherein R^2 and R^3 are as hereinbefore defined in relation to formula (I), or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II),



(II)

wherein R^2 and R^3 are as defined in relation to formula (I), with an acid and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

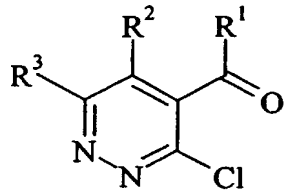
(iii) preparing an appropriate salt or solvate of the compound so formed.

The reaction between the compound of formula (II) and an acid is carried out under conventional conditions, optionally in the presence of a suitable solvent, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable acids include mineral acids, such as hydrobromic acid and hydrochloric acid. Suitably, the reaction is performed using the acid as a solvent. Suitable reaction temperatures include those in the range of 20°C to 220°C and, as appropriate, the reflux temperature of the reagents. Suitable reaction times are those in the range 0.5 to 24 hours, preferably 0.5 to 2 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, a mixture of the compound of formula (II) and hydrobromic acid are heated under reflux for 0.5 to 2 hours, preferably 1 hour, and then added to a suitable solvent such as water. The resulting solid is then filtered, washed with a suitable solvent, such as water, and dried *in vacuo*. Typically, the solid is then purified by column chromatography, using one or more suitable solvents, such as 1% v/v methanol in dichloromethane, to afford the desired compound of formula (I).

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) where R^1 is alkyl, hydroxyalkyl, aryl,

arylalkoxyalkyl or heteroaryl wherein the heteroaryl group may be optionally substituted by alkoxy or =O and wherein R^2 and R^3 are as hereinbefore defined in realtion to formula (I), or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (III),



(III)

wherein R^1, R^2 and R^3 are as defined in relation to formula (I), with hydrazine or a hydrate thereof and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed.

The reaction between the compound of formula (III) with hydrazine or a hydrate thereof is carried out under conventional conditions, in the presence of a suitable solvent, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable solvents include alcohols such as ethanol. Suitable reaction temperatures include those in the range of 0°C to 150°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 0.5 to 60 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, hydrazine hydrate is added to a stirred suspension of the compound of formula (III) in ethanol at 0°C. The reaction mixture is then heated at 60°C, for 3 hours and then allowed to cool. The resulting solution is evaporated to dryness and the solid residue purified, typically by chromatography on silica gel with one or more

suitable solvents, such as 10% diethyl ether in dichloromethane, to afford the desired compound of formula (I).

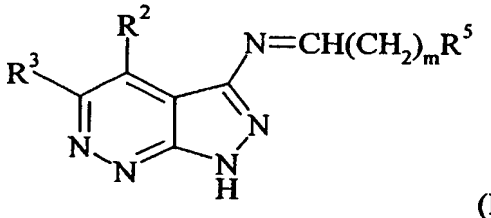
In a further preferred aspect, an aqueous solution of hydrazine is added with ethanol to a stirred solution compound of formula (II) at 0°C. The mixture is stirred at ambient temperature for 0.5 hours and is subsequently heated to 60°C, for 0.5 hours. After cooling to ambient temperature, the resulting mixture is evaporated to dryness and water added. After standing for 14 hours, the solid is collected, preferably by filtration, dried and sonicated in a suitable solvent such as dichloromethane. The resulting solid is collected, preferably by filtration, washed with a suitable solvent such as dichloromethane, and dried, preferably *in vacuo* to afford the desired compound of formula (I).

In still a further preferred aspect, a mixture of a compound of formula (III) and hydrazine hydrate in ethanol is heated under reflux for 48 hours. Upon cooling, the solvent is removed *in vacuo* and the residue is dissolved in a mixture of water and ethyl acetate. The layers are separated and the organic layer is washed successively with water, water at pH 3 (hydrochloric acid) and water and brine. The resulting solution is dried over magnesium sulfate and reduced in vacuo to a solid. The solid is purified by silica gel chromatography using one or more suitable solvents, such as dichloromethane-diethyl ether (gradient from 10:1 to 1:1 v/v) to afford the desired compound of formula (I).

In still a further preferred aspect, a mixture of a compound of formula (III) and hydrazine hydrate in ethanol is heated under reflux for 20 hours. The resulting mixture is concentrated *in vacuo* and the residue is dissolved in toluene and heated under reflux for a further 24 hours. The toluene is removed *in vacuo* and the residue is treated with a mixture of water and dichloromethane. The resulting mixture is filtered, the layers separated, and the organic layer is washed with brine and dried over magnesium sulfate. The solution is concentrated *in vacuo* and the resulting oil purified by silica gel chromatography using one or more suitable solvents, such as dichloromethane-diethyl ether (20:1 to 3:1 v/v) to afford the desired compound of formula (I).

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) where R^1 is $-NH(CH_2)_nR^5$, and wherein R^2, R^3 and R^5 are as hereinbefore defined in relation to formula (I), or a salt

thereof and/or a solvate thereof, which process comprises reacting a compound of formula (IV),



(IV)

wherein R^2, R^3 and R^5 are as defined in relation to formula (I), and m is n-1, with a reducing agent and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

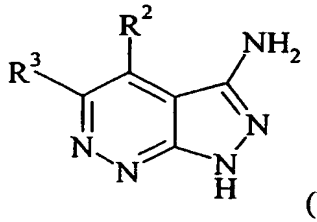
(iii) preparing an appropriate salt or solvate of the compound so formed.

The reaction between the compound of formula (IV) with a reducing agent is carried out under conventional conditions, in the presence of a suitable solvent, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable reducing agents include sodium borohydride, sodium triacetoxyborohydride and (polystyrylmethyl) trimethylammonium cyanoborohydride. A suitable solvent is dry tetrahydrofuran. Suitable reaction temperatures include those in the range of 20°C to 150°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 48 to 132 hours. Suitably the reaction is performed in an inert atmosphere, such as argon. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, a mixture of the compound of formula (IV), sodium triacetoxyborohydride and acetic acid in dry tetrahydrofuran are stirred at ambient temperature for 120 hours under argon. A suitable aqueous base, such as saturated

sodium bicarbonate and a suitable solvent, such as ethyl acetate, are added to the resulting reaction mixture. The organic layer is separated and the aqueous layer re-extracted with a suitable solvent, such as ethyl acetate. The combined extracts are dried with a suitable drying agent, such as magnesium sulfate and concentrated. The desired compound of formula (I) is afforded following purification by column chromatography using one or more suitable solvents, such as 2% v/v methanol in dichloromethane).

Compounds of formula (I) where R^1 is $-NH(CH_2)_nR^5$, and wherein R^2, R^3 and R^5 are as hereinbefore defined and n is 1, or a salt thereof and/or a solvate thereof, may also be prepared by reacting a compound of formula (V),



(V)

wherein R^2 and R^3 are as defined in relation to formula (I), with an aldehyde, R^5CHO, wherein R^5 is defined in relation to formula (I), and a reducing agent and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed;

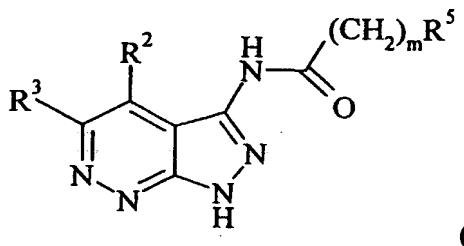
thereby constituting a further aspect of the present invention.

The reaction between the compound of formula (V) with an aldehyde, R^5CHO, and a reducing agent is carried out under conventional conditions, in the presence of a suitable solvent, optionally in the presence of a suitable dehydrating agent, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable dehydrating agents are molecular sieves. Suitable reducing agents include sodium borohydride, sodium triacetoxyborohydride and (polystyrylmethyl) trimethylammonium cyanoborohydride. A suitable solvent is n-butanol. Suitable reaction temperatures include those in the range of 20°C to 220°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 12 to 48

hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, n-butanol and molecular sieves are added to a mixture of the compound of formula (V) and an aldehyde, R^5CHO, such as 4-chlorobenzaldehyde, with stirring. The reaction mixture is heated under reflux for 24 hours. After cooling to room temperature the solvent is removed *in vacuo*, and a suitable solvent, such as anhydrous tetrahydrofuran is added. To this solution, sodium borohydride is added and the mixture heated at 50°C for 16 hours. The mixture is then filtered and concentrated, then redissolved in a suitable solvent, such as methanol, and filtered again. The filtrate is concentrated and a suitable solvent, such as dichloromethane, is added. The mixture is filtered, and the resulting solid dissolved in a suitable solvent, such as methanol, and purified by preparative HPLC (C18 column, gradient of 10-90% acetonitrile containing 0.01% trifluoroacetic acid) in water (containing 0.1% trifluoroacetic acid). The resulting solid is dissolved in methanol and further purified by passing it through a suitable SCX cartridge, eluting with 2N methanolic ammonia solution. The resulting solution is evaporated and the solid residue purified by silica gel chromatogrpahy using one or more suitable solvents, such as 2% methanol in dichloromethane), to afford the desired compound of formula (I).

Compounds of formula (I) where R^1 is $-NH(CH_2)_nR^5$ and wherein R^2, R^3, R^5 and n are as hereinbefore defined, or a salt thereof and/or a solvate thereof, may also be prepared by reaction of a compound of formula (VI),



(VI)

wherein R^2 and R^3 are as defined in relation to formula (I) and m is n-1, and a reducing agent and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed;

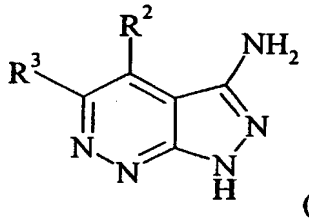
thereby constituting a further aspect of the present invention.

The reaction between the compound of formula (VI) with a reducing agent is carried out under conventional conditions, in the presence of a suitable solvent, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. A suitable reducing agent is lithium aluminium hydride. Suitable solvents include dry tetrahydrofuran and 1,4-dioxan. Suitable reaction temperatures include those in the range of 20°C to 220°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 1 to 48 hours, preferably 2 to 24 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, 1.0M lithium aluminium hydride in tetrahydrofuran is added slowly to a solution of the compound of formula (VI) in 1,4-dioxan with stirring. The reaction mixture is then heated under reflux for 2 hours, allowed to cool, and then water is added. The resulting solution is concentrated and the residue purified by column chromatography using one or more suitable solvents, such as 4% v/v methanol in dichloromethane), to afford the desired compound of formula (I).

In a further preferred aspect, 1.0M lithium aluminium hydride in tetrahydrofuran is added slowly to a solution of the compound of formula (VI) in dry tetrahydrofuran at ambient temperature. The reaction mixture is allowed to stir at ambient temperature for a further 24 hours. The reaction is suitably quenched by the successive addition of water, aqueous sodium hydroxide and water. The mixture is filtered and concentrated *in vacuo*, and the residue purified by column chromatography using one or more suitable solvents, such as dichloromethane to 2% methanol/dichloromethane), to afford the desired compound of formula (I).

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) where R^1 is $-NHR^4$ where R^4 is $-CHR^8R^9$, wherein R^8 and R^9 are independently alkyl, or, R^8 and R^9 together with the carbon atom to which they are attached may form an optionally substituted cyclic group which may be fused to an aryl ring to form a bicyclic moiety, and wherein R^2 and R^3 are as hereinbefore defined, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (V),



(V)

wherein R^2 and R^3 are as defined in relation to formula (I), with

(a) a ketone, $R^8R^9C=O$ wherein R^8 and R^9 are independently alkyl, or, R^8 and R^9 together with the carbon atom to which they are attached may form a cyclic group; and

(b) a reducing agent and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

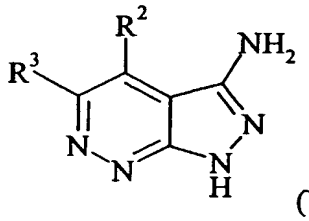
(iii) preparing an appropriate salt or solvate of the compound so formed.

The reaction between the compound of formula (V) with a ketone, $R^8R^9C=O$ and a reducing agent is carried out under conventional conditions, in the presence of a suitable solvent, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. A suitable solvent is dry methanol. A suitable ketone is cyclopentanone. A suitable reducing agent is (polystyrylmethyl) trimethylammonium cyanoborohydride. Suitable reaction temperatures include those in the range of 20°C to 120°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 12 to 48 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths

respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, to a stirred suspension of a compound of formula (V), a suitable ketone, $R^8R^9C=O$, such as cyclopetanone and (polystyrylmethyl) trimethylammonium cyanoborohydride in dry methanol is added acetic acid. The reaction mixture is stirred under ambient conditions for 18 hours. The resulting mixture is filtered and concentrated *in vacuo* to afford a crude oil which is triturated with a suitable solvent, such as dichloromethane, and dried *in vacuo* to afford the desired compound of formula (I).

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) where R^1 is $-N=CHR^6$ and wherein R^2, R^3 and R^6 are as hereinbefore defined, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (V),



(V)

wherein R^2 and R^3 are as defined in relation to formula (I), with an aldehyde, R^6CHO, where R^6 is as hereinbefore defined, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed.

The reaction between the compound of formula (V) with an aldehyde, R^6CHO, is carried out under conventional conditions, in the presence of a suitable solvent, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. A suitable solvent is n-butanol. A suitable aldehyde is benzaldehyde. Suitable reaction temperatures include those in the range of 20°C to

220°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 12 to 48 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, a solution of a compound of formula (V) and a suitable aldehyde, such as benzaldehyde, in n-butanol is stirred under reflux for 40 hours. The resulting solution is allowed to cool and concentrated *in vacuo*. The crude product is purified by column chromatography using one or more suitable solvents, such as 2% v/v methanol in dichloromethane), to afford the desired compound of formula (I).

The above-mentioned conversions of a compound of formula (I) into another compound of formula (I) include any conversion which may be effected using conventional procedures, but in particular the said conversions include any combination of:

(i) converting one group R^1 into another group R^1;

(ii) converting one group R^2 into another group R^2;

(iii) converting one group R^3 into another group R^3;

The above-mentioned conversions (i), (ii) and (iii) may be carried out using any appropriate method under conditions determined by the particular groups chosen.

Suitable conversions of one group R^1 into another group R^1, as in conversion (i), include:

(a) converting a group R^1 which represents halo, such as bromo, into another group R^1 which represents $-NHR^4$ where R^4 represents heteroaryl, such as –NH(3-pyridyl). Such a conversion may be performed using an appropriate conventional amination procedure, for example, by treating a compound of formula (I) wherein R^1 is halo, such as bromo, with a suitable nucleophile, such as 3-aminopyridine hydrochloride.

(b) converting a group R^1 which represents heteroaryl, such as 3-(2-MeO-pyridyl), into another group R^1 which also represents heteroaryl, such as 3-(2-pyridonyl). Such a conversion may be performed using an appropriate conventional dealkylation procedure,

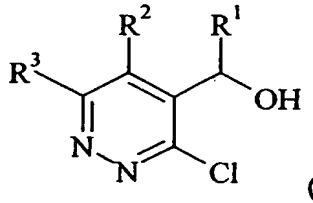
for example, by treating a compound of formula (I) wherein R^1 is heteroaryl, such as 3-(2-MeO-pyridyl), with a suitable acid, such as hydrobromic acid.

(c) converting a group R^1 which represents arylalkoxyalkyl, such as $-CH_2OCH_2Ph$, into another group R^1 which represents hydroxyalkyl, such as $-CH_2OH$. Such a conversion may be performed using an appropriate conventional ether cleavage procedure, for example, by treating a compound of formula (I) wherein R^1 is arylalkoxyalkyl, such as $-CH_2OCH_2Ph$, with a suitable reagent for ether cleavage, such as trimethylsilyl iodide.

The above-mentioned conversions may as appropriate be carried out on any of the intermediate compounds mentioned herein.

Compounds of formula (II) may be prepared by diazotisation of a compound of formula (V) under standard conditions, for example, by treatment of the compound of formula (V) with sulphuric acid and sodium nitrate.

Compounds of formula (III) may be prepared by reaction of a compound of formula (VII),



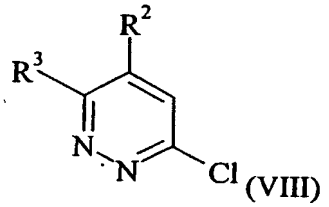
(VII)

wherein, R^1, R^2 and R^3 are as defined in relation to formula (I), with an oxidising agent.

The reaction between the compound of formula (VII) and an oxidising agent is carried out at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable oxidising reagents are MnO_2 or a mixture of oxalyl chloride and dimethylsulfoxide. Suitable reaction temperatures include those in the range 25 to –85 °C. A suitable solvent is dichloromethane. Suitable reaction times are those in the range 0.5-12 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction product may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, oxalyl chloride is dissolved in dry dichloromethane, cooled to –70 °C and dimethylsulphoxide in dichloromethane is added, keeping the temperature below –65 °C. The mixture is stirred, and a solution of a compound of formula (VII) in dicholoromethane is added. The mixture is stirred for a suitable period of time, such as 15 minutes, and then a suitable base, such as triethylamine is added. The reaction is stirred for a further period of time, suitably for five minutes, at –65 °C, and is then allowed to warm to room temperature. Water is added to the resulting reaction mixture, which is separated, and the organic layer is washed successively with water, water at pH3 (hydrochloric acid), water and brine. The resulting solution is dried with a suitable drying agent such as magnesium sulfate and evaporated *in vacuo* to afford the desired compound of formula (III).

Compounds of formula (VII) may be prepared by reaction of a compound of formula (VIII),


(VIII)

wherein R^2 and R^3 are as defined in relation to formula (I), with a base and an aldehyde, R^1CHO, where R^1 is as defined in relation to formula (I).

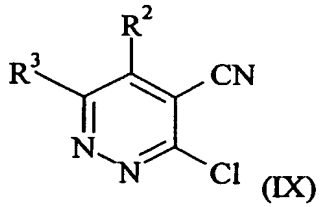
The reaction between the compound of formula (VIII), a base and an aldehyde, R^1CHO is carried out at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. A suitable base is lithium 2,2,6,6-tetramethylpiperidide. Suitable reaction temperatures include those in the range 25 to –85 °C. A suitable solvent is tetrahydrofuran. Suitable reaction times are those in the range 0.5-12 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction product may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, a solution of n-butyllithium is added to dry tetrahydrofuran at –30 °C under argon, and warmed to 0 °C. 2,2,6,6-tetramethylpiperidine is added to the solution, which is maintained at 0°C for a suitable period of time, such as 30 minutes. The reaction mixture is cooled to –75 °C and a compound of formula (VIII) is added. After 1 hour the reaction mixture is allowed to warm to room temperature. The mixture is then made slightly basic by the addition of aqueous sodium bicarbonate and is concentrated *in vacuo*. Water and dichloromethane are added, the mixture is separated, and the organic layer is washed successively with water, water at pH 3 (hydrochloric acid), water and brine. The resulting solution is dried with a suitable drying agent, such as magnesium sulfate, and evaporated *in vacuo* to afford an oil. The oil is purified by silica gel chromatography, using one or more suitable solvents, such as dichloromethane-diethyl ether (gradient from 50:1 to 10:1 v/v). The resulting oil is triturated with a mixture of hexane and ether to afford the desired compound of formula (VIII).

Compounds of formula (VIII) are either commercially available or are prepared by analogy with known conventional procedures such as those in standard reference texts of synthetic methodology, for example, *J. March, Advanced Organic Chemistry, 4th Edition, 1992, Wiley Interscience.*

Compounds of formula (IV) may be prepared by reaction of a compound of formula (V) with a suitable aldehyde. Such methods are analogous to those described hereinbefore for the preparation of a compound of formula (I) where R^1 is $-N=CHR^6$.

Compounds of formula (V) may be prepared by reaction of a compound of formula (IX),



(IX)

wherein;

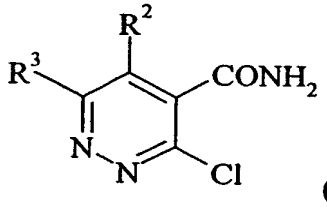
R^2 and R^3 are as defined in formula (I), with hydrazine or a hydrate thereof.

The reaction between the compound of formula (IX) and hydrazine, or a hydrate thereof, is carried out in a suitable solvent at a suitable temperature providing a suitable

rate of formation of the required product, generally an elevated temperature, over a suitable reaction time. A suitable solvent is ethanol. Suitable reaction temperatures include those in the range of 60°C to 220°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 1-48 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled, the product isolated by filtration, and dried. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, hydrazine hydrate is added to a stirred solution of the compound of formula (IX) in ethanol. The reaction mixture is stirred under reflux for 1 hour and is cooled. The resulting solution is concentrated *in vacuo*, triturated with water, and filtered and dried to afford the desired compound of formula (VIII).

Compounds of formula (IX) may be prepared by reaction of a compound of formula (X),



(X)

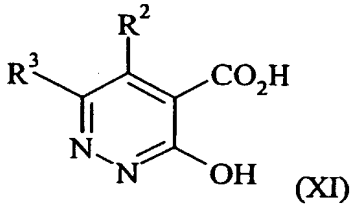
wherein, R^2 and R^3 are as defined in formula (I), with phosphoryl chloride.

The reaction between the compound of formula (X) and phosphoryl chloride is carried out optionally in a suitable solvent at a suitable temperature providing a suitable rate of formation of the required product, generally an elevated temperature, over a suitable reaction time. Suitable reaction temperatures include those in the range of 60°C to 220°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 1-48 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled and evaporated, and the residue dissolved in a suitable solvent and washed with a suitable aqueous base. The organic solution is then dried with a suitable drying agent and evaporated. Conventional methods of heating and cooling may be employed, for example thermostatically

controlled oil baths and ice/salt baths respectively. The reaction products may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, the compound of formula (X) is dissolved in phosphoryl chloride and heated under reflux for 3 hours. The resulting mixture is cooled and evaporated, and the residue is dissolved in dichloromethane and washed with saturated sodium hydrogen carbonate solution. The organic solution is then dried with magnesium sulfate and evaporated to afford the desired compound of formula (IX).

Compounds of formula (X) may be prepared by reaction of a compound of formula (XI),



(XI)

wherein; R^2 and R^3 are as defined in formula (I), with,

1) phosphoryl chloride; followed by,

2) aqueous ammonia.

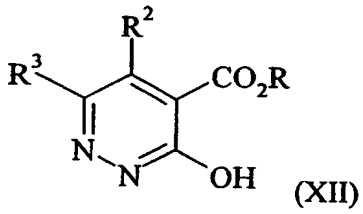
The reaction between the compound of formula (XI) and phosphoryl chloride (according to step 1 above), is carried out optionally in a suitable solvent at a suitable temperature providing a suitable rate of formation of the required product, generally an elevated temperature, over a suitable reaction time, optionally in the presence of a suitable catalyst. Suitable reaction temperatures include those in the range of 60°C to 220°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 1-48 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled and evaporated. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively.

The reaction between the product of step (1) above and aqueous ammonia (according to step 2 above), is carried out optionally in a suitable solvent at a suitable temperature providing a suitable rate of formation of the required product, generally an

elevated temperature, over a suitable reaction time. Suitable reaction temperatures include those in the range of 20°C to 100°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 1-48 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is diluted with water and extracted with a suitable solvent. The product is isolated from the organic solution by drying with a suitable drying agent followed by evaporation. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, the compound of formula (XI) is dissolved in phosphoryl chloride containing 3 drops of dry N,N-dimethylformamide and heated at 80°C for 4 hours, then cooled and evaporated. The residue is dissolved in dry THF and added with vigorous stirring to concentrated aqueous ammonia solution. After 1 hour the mixture is diluted with water, extracted with ethyl acetate and the organic solution washed with brine, dried over magnesium sulfate and evaporated to afford the desired compound of formula (X). The crude product may be used without purification.

Compounds of formula (XI) may be prepared by reaction of a compound of formula (XII),



(XII)

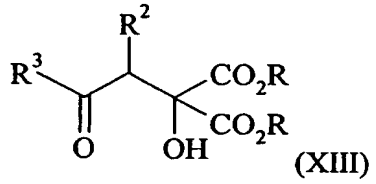
wherein; R^2 and R^3 are as defined in formula (I), and R represents a straight or branched chain alkyl moiety, with sodium hydroxide.

The reaction between the compound of formula (XII) and sodium hydroxide is carried out optionally in a suitable solvent at a suitable temperature providing a suitable rate of formation of the required product, generally an elevated temperature, over a suitable reaction time. A suitable solvent is ethanol. Suitable reaction temperatures include those in the range of 20°C to 100°C and, as appropriate, the reflux temperature of

the solvent. Suitable reaction times are those in the range 1-48 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled and evaporated, and the residue diluted with water and filtered. Acidification of the filtrate affords a precipitate, which is filtered, washed with water and dried. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, the compound of formula (XII) is dissolved in ethanol and aqueous sodium hydroxide solution and heated at reflux for 2 hours, then cooled and evaporated. The residue is diluted with water, filtered, and the filtrate acidified with 2M HCl to afford a precipitate which is filtered, washed with water and dried *in vacuo* to afford the desired compound of formula (XI). The crude product may be used without purification.

Compounds of formula (XII) may be prepared by reaction of a compound of formula (XIII),



(XIII)

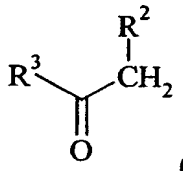
wherein, R^2 and R^3 are as defined in formula (I), and R represents a straight or branched chain alkyl moiety, with hydrazine, or a hydrate, or the hydrochloride thereof.

The reaction between the compound of formula (XIII) and hydrazine, or a hydrate, or the hydrochloride thereof, is carried out optionally in a suitable solvent at a suitable temperature providing a suitable rate of formation of the required product, generally an elevated temperature, over a suitable reaction time. A suitable solvent is ethanol. Suitable reaction temperatures include those in the range of 20°C to 100°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 24-120 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled and evaporated to dryness. Conventional

methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, the compound of formula (XIII) is dissolved in ethanol containing hydrazine monohydrochloride and heated at reflux for 96 hours, then cooled and evaporated to dryness, to afford the desired compound of formula (XII). The crude product may be used without purification.

Compounds of formula (XIII) may be prepared by reaction of a compound of formula (XIV),



(XIV)

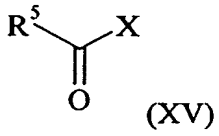
wherein, R^2 and R^3 are as defined in formula (I), with a di-alkyl ketomalonate.

The reaction between the compound of formula (XIV) and di-alkyl ketomalonate is carried out optionally in a suitable solvent at a suitable temperature providing a suitable rate of formation of the required product, generally an elevated temperature, over a suitable reaction time. Suitable reaction temperatures include those in the range of 60°C to 200°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 24-96 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is diluted with a suitable solvent and purified by chromatography, for example, silica gel chromatography. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively.

In a preferred aspect, the compound of formula (XIV) and diethyl ketomalonate are heated at 140°C for 48 hours, then cooled. The reaction mixture is diluted with toluene and chromatographed on silica gel using 20% v/v ethyl acetate in hexane to afford the desired compound of formula (XIII).

Compounds of formula (XIII) are either commercially available or are prepared by analogy with known conventional procedures such as those in standard reference texts of synthetic methodology, for example, *J. March, Advanced Organic Chemistry, 4th Edition, 1992, Wiley Interscience.*

Compounds of formula (VI) may be prepared by reaction of a compound of formula (V) with a compound of formula (XV),



(XV)

wherein, R^5 is a defined in relation to formula (I), and X is halo, for example, chloro.

The reaction between the compound of formula (V) and a compound of formula (XV) is carried out in a suitable solvent at a suitable temperature providing a suitable rate of formation of the required product, generally an elevated temperature, over a suitable reaction time. A suitable solvent is pyridine. Suitable reaction temperatures include those in the range of 60°C to 200°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 24-96 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively.

In a preferred aspect, a solution of a compound of formula (V) and a compound of formula (XV) in pyridine is heated under reflux, with stirring, for 24 hours. The resulting solution is cooled and concentrated *in vacuo*. The residue is purified by column chromatography using one or more suitable solvents, such as 2%v/v methanol in dichloromethane, to afford the desired compound of formula (VI).

Certain compounds of formula (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) are believed to be novel and accordingly form a further aspect of the present invention.

Compounds of formulae (I), (IA), (IB), (IV), (V), (VI), (XI) and (XII) may exist as tautomers. The present invention encompasses all tautomeric forms of the compounds of (I), (IA), (IB), (IV), (V), (VI), (XI) and (XII).

As stated above, the compounds of formula (I), or pharmaceutically acceptable salts or solvates thereof, are indicated to be useful as inhibitors of glycogen synthase kinase-3.

The invention therefore provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an inhibitor of GSK-3.

Accordingly, the present invention also provides a method for the treatment of conditions associated with a need for inhibition of GSK-3 such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency, which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The present invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as an inhibitor of glycogen synthase kinase-3, and especially for use in the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia,

Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

In a further aspect of this invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

Preferably, the compounds of formula (I), or pharmaceutically acceptable salts or solvates thereof, are administered as pharmaceutically acceptable compositions.

Accordingly, the invention also provides a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The active compounds are usually administered as the sole medicament agent but they may be administered in combination with other medicament agents as dictated by the severity and type of disease being treated.

The said combination comprises co-administration of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and an additional medicament agent or the sequential administration of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and the additional medicament agent.

Co-administration includes administration of a pharmaceutical composition which contains both a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and the additional medicament agent or the essentially simultaneous administration of separate pharmaceutical compositions of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and the additional medicament agent.

The compositions of the invention are preferably adapted for oral administration. However, they may be adapted for other modes of administration. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions. In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose. Preferably the composition are in unit dosage form. A unit dose will generally contain from 0.1 to 1000 mg of the active compound.

Generally an effective administered amount of a compound of the invention will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated and the weight of the sufferer. However, active compounds will typically be administered once or more times a day for example 2, 3 or 4 times daily, with typical total daily doses in the range of from 0.1 to 800 mg/kg/day.

Suitable dose forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium

starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulfate.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The formulations mentioned herein are carried out using standard methods such as those described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) or the above-mentioned publications.

Suitable methods for preparing and suitable unit dosages for the additional medicament agent, such as the antidiabetic agent mentioned herein include those methods and dosages described or referred to in the above-mentioned reference texts.

GSK-3 Assay

GSK-3 assays used to test the compounds of the invention include the following protocol which is based on the ability of the kinase to phosphorylate a biotinylated 26 mer peptide, Biot- KYRRAAVPPSPSLSRHSSPHQ(S)EDEEE, the sequence of which is derived from the phosphorylation site of glycogen synthase, where (S) is a pre-phosphorylated serine as in glycogen synthase *in vivo* and the three consensus sites for GSK-3 specific phosphorylation are underlined. The phosphorylated biotinylated peptide is then captured onto Streptavidin coated SPA beads (Amersham Technology), where the signal from the ^{33}P is amplified via the scintillant contained in the beads.

Using microtitre plates, GSK-3 was assayed in 50 mM MOPS buffer, pH 7.0, containing 5% glycerol, 0.01% Tween-20, 7.5 mM 2-mercaptoethanol, 10 mM magnesium acetate, 8 uM of the above peptide, and 10 uM [^{33}P]-ATP. After incubation at room temperature, the reaction was stopped by addition of 50 mM EDTA solution containing the Streptavidin coated SPA beads to give a final 0.2 mgs. Following centrifugation, the microtitre plates are counted in a Trilux 1450 microbeta liquid scintillation counter (Wallac). IC_{50} values are generated for each compound by fitting to a four parameter model.

The most potent compounds of the present invention show IC_{50} values in the range of 1 to 500 nM.

No adverse toxicological effects are expected for the compounds of the invention, when administered in accordance with the invention.

The following Descriptions and Examples illustrate the invention, but do not limit it in any way.

Synthetic Method A

Example 1

N-Benzyl-[5-(2-chlorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl]amine

A solution of N-benzylidene-[5-(2-chlorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl]amine (115.7 mg 0.35 mmol), sodium triacetoxyborohydride (700 mg, 3.30 mmol) and acetic acid (3 drops) in dry tetrahydrofuran (4 mL) was stirred at ambient temperature under an argon atmosphere for 5 days. Saturated sodium bicarbonate (5 mL) and ethyl acetate (5 mL) were added. The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (2x5 mL). The combined extracts were dried over magnesium sulfate and concentrated. Purification by column chromatography (2% v/v methanol in dichloromethane) afforded the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 336/338 ($C_{18}H_{14}ClN_5$ requires $[M+H]^+$ at m/z: 336/338.

^1H NMR δ (DMSO-d_6): 4.49 (2H, d), 7.2-7.5 (8H, m), 7.64 (2H, m), 8.35 (1H, s), 12.8 (1H, s).

Synthetic Method B

Example 2

N-Cyclopentylmethyl-[5-phenyl-1H-pyrazolo[3,4-c]pyridazin-3-yl] amine

1.0M Lithium aluminium hydride in tetrahydrofuran (0.35 mL, 0.35 mmol) was slowly added to a solution of N-[5-phenyl-1H-pyrazolo[3,4-c]pyridazin-3-yl]cyclopentanecarboxamide (40.7 mg, 0.13 mmol) in dioxan (1.8 mL). The reaction mixture was stirred at reflux for 2 hours, allowed to cool, a few drops of water added to decompose the excess lithium aluminium hydride and the solution concentrated. Purification by column chromatography (4% v/v methanol in dichloromethane) afforded the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 294 ($C_{17}H_{19}N_5$ requires $[M+H]^+$ at m/z: 294).

^1H NMR δ (DMSO-d_6): 1.38 (2H, m), 1.60-1.78 (4H, m), 1.85 (2H, m), 3.30 (2H, t), 6.63 (1H, s), 7.50 (2H, m), 7.62 (2H, m), 8.13 (2H, d), 8.66 (1H, s), 12.7 (1H, s).

The starting material for Example 2 may be prepared by the method of Description 1

Description 1

N-[5-Phenyl-1H-pyrazolo[3,4-c]pyridazin-3-yl]cyclopentanecarboxamide

A solution of 5-phenyl-1H-pyrazolo[3,4-c]pyridazin-3-ylamine(130 mg, 0.62 mmol) and cyclopentanecarbonyl chloride (82 mg, 0.62 mmol) in pyridine (0.6 mL) was stirred under reflux for 24 hours, allowed to cool and concentrated. Purification by column chromatography (2% v/v methanol in dichloromethane) afforded the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 308 ($C_{17}H_{17}N_5O$ requires $[M+H]^+$ at m/z: 308).

^{1}H NMR δ (DMSO-d_6): 1.55-1.88 (8H, m), 2.94 (1H, t), 7.46 (1H, m), 7.54 (2H, m), 8.06 (2H, d), 8.66 (1H, s), 11.0 (1H, s), 14.05 (1H, s).

Synthetic Method C

Example 3

A mixture of 3-bromo-5-phenyl-1H-pyrazolo[3,4-c]pyridazine (75 mg, 0.27 mmol) and 3-aminopyridine hydrochloride (91 mg, 0.55 mmol) was stirred at 170 degrees C for 20 hours then 3% sodium hydroxide solution added. The mixture was treated to pH 5 with acetic acid and the solid filtered, washed with water and dried under vacuum. Purification by column chromatography (4% v/v methanol in dichloromethane) afforded the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 289 ($C_{11}H_{12}N_6$ requires $[M+H]^+$ at m/z 289.

^{1}H NMR δ (DMSO-d_6): 7.35 (1H, m), 7.47 (1H, m), 7.57 (2H, m), 8.09 (3H, m), 8.17 (1H, d), 8.73 (1H, s), 8.85 (1H, s), 9.67 (1H, s), 13.45 (1H, s).

Synthetic Method D

Example 4

5-Chloro-3-phenyl-1H-pyrazolo[3,4-c]pyridazine

An aqueous solution of 80% hydrazine (0.24 g, 2.9 mmol) was added with ethanol (2 mL) to (3,6-dichloro-4-pyridazinyl)phenylmethanone (0.333g, 1.32 mmol, prepared by the method of A Turck et al. J. Het Chem 1990, 27, 1377) with stirring and cooling in an ice bath. The mixture was then stirred at room temperature for half an hour before heating at 60°C for a further half an hour. After cooling to room temperature the mixture was evaporated to dryness and water (1 mL) added. After standing overnight the resulting

solid was collected, dried and sonicated with dichloromethane (2 mL). The resulting solid was collected, washed with dichloromethane (2 mL) and dried to give the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 231/233 ($C_{11}H_7ON_4Cl$ requires $[M+H]^+$ at m/z 231/233).

^1H NMR δ (DMSO-d_6): 7.49 (1H, t), 7.52-7.62 (2H, m), 8.11 (2H, d), 8.77 (1H, s), 14.83 (1H, br s).

Synthetic Method E

Example 5

5-(3-Pyridyl)-1H-pyrazolo[3,4-c]pyridazine

3-Diazo-5-pyridin-3-yl-3H-pyrazolo[3,4-c]pyridazine (13 mg, 0.058 mmol) was heated at reflux in methanol for one hour and then allowed to cool. After evaporation to dryness the title compound was obtained as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 198 ($C_{10}H_7N_5$ requires $[M+H]^+$ at m/z 198).

^1H NMR δ (DMSO-d_6): 7.59 (1H, dd), 8.45(1H, finely coupled d; becomes s after D_2O shake), 8.52-8.6 (1H, m), 8.65-8.74 (1H, m), 8.78 (1H, s), 9.35 (1H, m), 14.6 (1H, br s, exchanges with D_2O).

Synthetic Method F

Example 6

N-Benzylidene-[5-(2-chlorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl]amine

A solution of 5-(2-chlorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-ylamine (150 mg, 0.61 mmol) and benzaldehyde (188 mg, 1.78 mmol) in n-butanol (4 mL) was stirred under reflux for 40 hours and concentrated. Purification by column chromatography (2% v/v methanol in dichloromethane) afforded the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 334/336 ($C_{18}H_{12}ClN_5$ requires $[M+H]^+$ at m/z 334/336).

^1H NMR δ (DMSO-d_6): 7.35 (5H, m), 7.5 (2H, m), 7.87 (2H, m), 8.45 (1H, s), 9.11 (1H, s), 14.3 (1H, s).

Synthetic Method G

Example 7

3,5-Diphenyl-1H-pyrazolo[3,4-c]pyridazine

Hydazine hydrate (0.29 g, 4.9 mmol) was added with stirring to an ice bath cooled suspension of 1-(3-chloro-6-phenylpyridazin-4-yl)-1-phenylmethanone (0.5 g, 1.7 mmol) in ethanol (2.5 mL). The mixture was then heated at 60°C for 3 hours and allowed to cool before evaporation to dryness. Purification by chromatography on silica gel with 10% diethyl ether in dichloromethane afforded the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 273 ($C_{17}H_{12}N_4$ requires $[M+H]^+$ at m/z 273).

^{1}H NMR δ (DMSO-d_6): 7.45-7.63 (6H, overlapping m), 8.22 (2H, apparent d), 8.31 (2H, apparent d), 8.88 (1H, s), 14.7 (1H,br s).

The starting material for Example 7 may be prepared according to Descriptions 2 below.

Description 2

1-(3-Chloro-6-phenylpyridazin-4-yl)-1-phenylmethanone

A solution of n-butyl lithium in hexane (1.92 mL, 10M, 19.2 mmol) was added to dry tetrahydrofuran (160 mL) at -30 °C under argon. The solution was warmed to 0 °C and dry 2,2,6,6-tetramethylpiperidine (3.64 mL, 21.6 mmol) added dropwise with stirring and then maintained at this temperature for half an hour before cooling to -70 °C. 3-Chloro-6-phenylpyridazine (2.0 g, 10.5 mmol) was added in one portion and stirring continued for a further 1.5 hours at this temperature. N-Methoxy-N-methylbenzamide (2.64g, 16 mmol) in dry tetrahydrofuran (20 mL) was added dropwise maintaining the temperature at -70 °C and then stirred for a further 1 hour. The reaction was quenched by the addition of a mixture of concentrated hydrochloric acid (8 mL), ethanol (8 mL) and tetrahydrofuran (32 mL) and then allowing to warm to room temperature. Saturated sodium bicarbonate solution was added to neutralise and then most of the organic solvents removed under reduced pressure. The residue was extracted with dichloromethane (100 mLx3) and the combined organics dried over anhydrous magnesium sulfate. The residue after evaporation of solvents was chromatographed on silica gel with dichloromethane and then 5% diethyl ether/dichloromethane to give the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 295/297 ($C_{17}H_{11}N_2OCl$ requires $[M+H]^+$ at m/z 295/297).

^1H NMR δ ($CDCl_3$): 7.49-7.6 (5H, m), 7.67-7.75 (1H, m), 7.78-7.88 (3H, m), 8.03-8.14 (2H, m).

Synthetic Method H

Example 8

3-Bromo-5-phenyl-1*H*-pyrazolo[3,4-c]pyridazine

A mixture of 3-diazo-5-phenyl-3H-pyrazolo[3,4-c]pyridazine (684 mg, 3.08 mmole) and 48% hydrobromic acid (3 mL) was heated under reflux for 1 hour then added to water (30 mL). The solid was filtered, washed with water and dried under vacuum. Purification by column chromatography (1% v/v methanol in dichloromethane) afforded the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 275/277 ($C_{11}H_7BrN_4$ requires $[M+H]^+$ at m/z 275/277).

^1H NMR δ (DMSO-d_6): 7.54-7.65 (3H, m), 8.32 (2H, d), 8.60 (1H, s), 15.0 (1H, s).

The starting material for Example 8 may be prepared by the method of Description 3

Description 3

3-Diazo-5-phenyl-3H-pyrazolo[3,4-c]pyridazine

To a suspension of 5-phenyl-1H-pyrazolo[3,4-c]pyridazin-3-ylamine(1.0 g, 4.73 mmol) in water (80 mL) at 5 degrees was added concentrated sulphuric acid followed by dropwise addition of 20% sodium nitrite solution (3.2 mL, 9.28 mmole) at 0 degrees C and the mixture stirred at 0 degrees for 30 minutes. The mixture was then basified with sodium carbonate and the solid filtered, washed with water and dried under vacuum at ambient temperature to afford the title compound as a solid.

^1H NMR δ (DMSO-d_6): 7.54-7.65 (3H, m), 8.22 (2H, d), 8.90 (1H, s).

Synthetic Method I

Example 9

3-Methyl-6-phenyl-1H-pyrazolo[3,4-c]pyridazine

A mixture of 3-chloro-4-acetyl-6-phenylpyridazine (568 mg, 2.44 mmol) and hydrazine hydrate (295 mg, 5 mmol) in ethanol (7mL) was heated at reflux for 2 days. The solvent was evaporated and the residue was dissolved in a mixture of water and ethyl acetate. The layers were separated and the organic layer was washed successively with water, water at pH3 (hydrochloric acid), water and brine, dried over magnesium sulfate and evaporated to a solid. This was chromatographed on silica gel using dichloromethane-diethyl ether (gradient from 10:1 to 1:1 v/v) as eluent to afford the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 211 ($C_{12}H_{10}N_4$ requires $[M+H]^+$ at m/z 211).

^1H NMR δ (DMSO-d_6): 2.61 (3H, s), 7.50 (3H, m), 8.20 (2H, m), 8.68 (1H, s), 14.0 (1H, s).

The starting material for Example 9 may be prepared by Descriptions 4, 5 below

Description 4

3-Chloro-4-(1-hydroxy)ethyl-6-phenylpyridazine

A solution of n-butyllithium (1.6M in hexane, 4.5 mL, 7.2 mmol) was added to dry tetrahydrofuran (60 mL) at –30°C under argon and warmed to 0°C. 2,2,6,6-Tetramethylpiperidine (1.35 mL, 8 mmol) was added and the solution was held at 0°C for 30 mins. It was then cooled to –70°C and solid 3-chloro-6-phenylpyridazine (953 mg, 5 mmol) was added in one portion and the mixture was stirred at –70°C for 1.5 hours. Acetaldehyde (2.8 mL, 50 mmol) was added and stirring continued at –70°C for 1 hour. A mixture of concentrated hydrochloric acid (3 mL), ethanol (3 mL) and tetrahydrofuran (12 mL) was added and the mixture allowed to warm to room temperature over 30 mins. The mixture was made slightly basic with saturated aqueous sodium bicarbonate and evaporated to low volume. The residue was extracted with dichloromethane, dried over magnesium sulfate and evaporated to dryness. The residue was triturated with a small amount of dichloromethane to give the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 235/237 ($C_{12}H_{11}ClN_2O$ requires $[M+H]^+$ at m/z 235/237).

^1H NMR δ (DMSO-d_6): 1.43 (3H, d), 4.96 (1H, m), 5.83 (1H, d), 7.58 (3H, m), 8.13 (2H, m), 8.27 (1H, s).

Description 5

3-Chloro-4-acetyl-6-phenylpyridazine

Oxalyl chloride (825 mg, 6.5 mmol) was dissolved in dry dichloromethane (15 mL), cooled to –65°C and dimethylsulphoxide (0.5 mL, 7 mmol) was added over 1 min keeping the temperature below –60°C. The mixture was stirred at –65°C for 5 mins then a solution of 3-Chloro-4-(1-hydroxy)ethyl-6-phenylpyridazine (755 mg, 3.22 mmol) in dimethylsulphoxide (2.5 mL) was added rapidly. The temperature rose to –20°C and the mixture was maintained at this temperature for 15 mins. Triethylamine (4.5 mL, 36 mmol) was added below –10°C and the mixture was stirred at –20°C for 5 mins then allowed to warm to room temperature over 1 hour. Water (30 mL) was added, separated and the organic layer washed successively with water, water at pH3 (hydrochloric acid), water and brine, dried over magnesium sulfate and evaporated to an oil. This was dissolved in ether giving a solution from which a solid rapidly precipitated. This was filtered off and dried to give the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 233/235 ($C_{12}H_9ClN_2O$ requires $[M+H]^+$ at m/z 233/235).

^1H NMR δ (DMSO-d_6): 2.73 (3H, s), 7.61 (3H, m), 8.20 (2H, m), 8.56 (1H, s).

Synthetic Method J

Example 12

3-(5-Phenyl-1H-pyrazolo[3,4-c]pyridazin-3-yl)-1H-pyridin-2-one

3-(2-Methoxypyrid-3-yl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine (20 mg, 0.066 mmol) was heated at 100 °C in 48% hydrobromic acid (2 mL) for 8 hours and, after cooling, the resulting mixture was neutralised with saturated sodium bicarbonate, diluting with water (10 mL). Attempted extraction with dichloromethane gave a solid on the interface which was collected and combined with the dichloromethane extracts. The minimum volume of methanol was added to effect solution, which was then dried with anhydrous magnesium

sulfate. After filtration and evaporation to dryness the title compound was obtained as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 290 ($C_{16}H_{11}N_5O$ requires $[M+H]^+$ at m/z 290).

^1H NMR δ (DMSO-d_6): 6.42 (1H, t), 7.42-7.68 (4H, m), 8.02-8.25 (3H, m), 8.89 (1H, s), 12.06 (1H, br s), 14.62 (1H, br s).

Synthetic Method K

Example 13

3-Benzyloxymethyl-5-phenyl-1H-pyrazolo[3,4-c]pyridazine

A mixture of 3-chloro-4-benzyloxyacetyl-6-phenylpyridazine (3.18 g, 9.39 mmol) and hydrazine hydrate (1.12 g, 19 mmol) in ethanol (25 mL) was heated at reflux for 20 hours. The solvent was evaporated and the residue was dissolved in toluene (25 mL) and refluxed for a further 24 hours. The toluene was evaporated and the residue taken up in a mixture of water and dichloromethane. The mixture was filtered, the layers separated and the organic layer was washed with brine, dried over magnesium sulfate and evaporated to an oil. Chromatography on silica gel using dichloromethane-diethyl ether (gradient from 20:1 to 3:1 v/v) as eluent afforded the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 317 ($C_{19}H_{16}N_4O$ requires $[M+H]^+$ at m/z 317).

^1H NMR δ (DMSO-d_6): 4.63 (2H, s), 4.97 (2H, s), 7.30 (5H, m), 7.55 (3H, m), 8.15 (2H, m), 8.60 (1H, s), 14.45 (1H, s).

The starting material for Example 13 was prepared by the methods of Descriptions 6 and 7

Description 6

3-Chloro-4-(2-benzyloxy-1-hydroxy)ethyl-6-phenylpyridazine

A solution of n-butyllithium (1.6M in hexane, 21 mL, 33 mmol) was added to dry tetrahydrofuran (160mL) at –30°C under argon and warmed to 0°C. 2,2,6,6-Tetramethylpiperidine (6.2 mL, 37 mmol) was added and the solution was held at 0°C for 30 mins. It was then cooled to –75°C and solid 3-chloro-6-phenylpyridazine (4.19g, 22 mmol) was added in one portion and the mixture was stirred at –75°C for 1.5 hours. Benzyloxyacetaldehyde (4.6 mL, 33 mmol) was added and stirring continued at –75°C

for 1 hour then the mixture was allowed to warm to room temperature over 30 mins. The mixture was made slightly basic with saturated aqueous sodium bicarbonate and evaporated to low volume. Water and dichloromethane were added, separated and the organic layer washed successively with water, water at pH3 (hydrochloric acid), water and brine, dried over magnesium sulfate and evaporated to an oil. This was chromatographed on silica gel using dichloromethane-diethyl ether (gradient from 50:1 to 10:1 v/v) as eluent to give an oil which on trituration with a mixture of hexane and ether gave the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 341/343 ($C_{19}H_{17}ClN_2O_2$ requires $[M+H]^+$ at m/z 341/343).

Description 7

3-Chloro-4-benzyloxyacetyl-6-phenylpyridazine

Oxalyl chloride (1.40 g, 11 mmol) was dissolved in dry dichloromethane (75 mL), cooled to –70°C and dimethylsulphoxide (1.72 g, 22 mmol) in dichloromethane (6 mL) was added over 1 min keeping the temperature below –65°C. The mixture was stirred at –65°C for 2 mins then a solution of 3-chloro-4-(2-benzyloxy-1-hydroxy)ethyl-6-phenylpyridazine (3.14 g, 9.2 mmol) in dichloromethane (15 mL) was added over 3 mins. The mixture was stirred at –65°C for 15 mins then triethylamine (6.4 mL, 46 mmol) was added. Stirred at –65°C for 5 mins then allowed to warm to room temperature over 1 hour. Water (75 mL) was added, separated and the organic layer washed successively with water, water at pH3 (hydrochloric acid), water and brine, dried over magnesium sulfate and evaporated to give the title compound as an oil.

MS (APCI +ve): $[M+H]^+$ at m/z 339/341 ($C_{19}H_{15}ClN_2O_2$ requires $[M+H]^+$ at m/z 339/341).

^1H NMR δ (DMSO-d_6): 4.54 (2H, s), 4.85 (2H, s), 7.30 (5H, m), 7.60 (3H, m), 8.15 (2H, m), 8.59 (1H, s).

Synthetic Method L

Example 14

3-Hydroxymethyl-5-phenyl-1H-pyrazolo[3,4-c]pyridazine

3-Benzyloxymethyl-5-phenyl-1H-pyrazolo[3,4-c]pyridazine (95 mg, 0.3 mmol) was dissolved in dry dichloromethane (3 mL), cooled in ice and a solution of trimethylsilyl iodide (72 mg, 0.36 mmol) in dichloromethane (0.5 mL) was added dropwise over 2 mins. The mixture was stirred at room temperature for 3 hours, more trimethylsilyl iodide (281 mg, 1.4 mmol) was added and the mixture was stirred at room temperature for 3 days. Methanol (0.5 mL) was added, stirred for 2 mins then dichloromethane (10 mL) and water (10 mL) added. The mixture was made basic with sodium bicarbonate and the organics evaporated. The resulting suspension was filtered and the solid was chromatographed on silica gel using dichloromethane-methanol (gradient from 50:1 to 5:1 v/v) as eluent to afford the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 227 ($C_{12}H_{10}N_4O$ requires $[M+H]^+$ at m/z 227).

^{1}H NMR δ (DMSO-d_6): 4.89 (2H, d), 5.52 (1H, t), 7.55 (3H, m), 8.17 (2H, m), 8.67 (1H, s), 14.23 (1H, s).

Synthetic Method M

Example 28

Cyclopentyl-[5-(2,3-difluorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl]amine

To a strirred suspension of 5-(2,3-difluorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-ylamine (200 mg, 0.8 mmol), cyclopentanone (168 mg, 2 mmol) and (polystyrylmethyl) trimethylammonium cyanoborohydride (1 mmol / g) (400 mg, 1.6 mmol) in dry methanol (10 mL) was added acetic acid (0.2 mL). The suspension was stirred at room temperature for 18 hours. The reaction mixture was filtered and concentrated. The crude oil was triturated with dichloromethane, the resulting solid was collected and dried under vacuum to afford the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 316 ($C_{16}H_{15}F_2N_5$ requires $[M+H]^+$ at m/z 316).

^{1}H NMR δ (DMSO-d_6): 1.56-1.62 (m, 4 H), 1.71-1.73 (m, 2 H), 1.97-2.02 (m, 2 H), 4.00-4.09 (m, 1 H), 6.69-6.70 (d, 1 H), 7.38-7.40 (m, 1 H), 7.52-7.55 (m, 1 H), 7.82-7.85 (m, 1 H), 8.51 (s, 1 H), 12.85 (1H, br s)

The starting material for Example 28 may be prepared by Descriptions 8-13 below

Description 8

Diethyl 2-[2-(2,3-difluorophenyl)-2-oxoethyl]-2-hydroxymalonate

2',3'-Difluoroacetophenone (10.23 g, 65.6 mmol) and diethyl ketomalonate (15 mL, 98.4 mmol) were stirred at 140°C for 48 hours. The crude mixture was diluted with toluene and purified by chromatography on silica gel, eluting with 20% v/v ethyl acetate in hexane to afford the title compound as an oil.

^{1}H NMR δ ($CDCl_3$): 1.30 (6H, t), 3.84 (2H, d), 4.18 (1H, s), 4.31 (4H, q), 7.18 (1H, m), 7.39 (1H, q) and 7.62 (1H, t).

Description 9

Ethyl 6-(2,3-difluorophenyl)-3-hydroxypyridazine-4-carboxylate

Diethyl 2-[2-(2,3-difluorophenyl)-2-oxoethyl]-2-hydroxymalonate (18.50 g, 56.1 mmol) and hydrazine monohydrochloride (4.03 g, 58.8 mmol) were stirred at reflux in ethanol (300 mL) for 96 h, and then evaporated to dryness to afford the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 281 ($C_{13}H_{10}F_2N_2O_3$ requires $[M+H]^+$ 281).

^{1}H NMR δ ($CDCl_3$): 1.14 (3H, t), 4.45 (2H, q), 7.25 (2H, m), 7.51 (1H, t), 8.28 (1H, s) and 11.87 (1H, s).

Description 10

6-(2,3-Difluorophenyl)-3-hydroxypyridazine-4-carboxylic acid

Ethyl 6-(2,3-difluorophenyl)-3-hydroxypyridazine-4-carboxylate (8.00 g, 28.6 mmol) was stirred in ethanol (275 mL) and treated with a solution of sodium hydroxide (4.6 g, 115 mmol) in water (175 mL). The mixture was stirred at reflux for 2 hours, cooled, concentrated *in vacuo*, diluted with water to ca. 350 mL total volume and filtered. Acidification with 2M hydrochloric acid gave a precipitate which was filtered off, washed with water, and thoroughly dried *in vacuo* at 60°C to afford the title compound as a solid.

MS (APCI -ve): $[M-H]^-$ at m/z 251 ($C_{11}H_6F_2N_2O_3$ requires $[M-H]^-$ 251).

^{1}H NMR δ (DMSO-d_6): 7.37 (1H, m), 7.57 (2H, m), 8.28 (1H, d) and 14.3 (2H, broad).

Description 11

3-Chloro-6-(2,3-difluorophenyl)pyridazine-4-carboxamide

6-(2,3-Difluorophenyl)-3-hydroxypyridazine-4-carboxylic acid (3.00 g, 11.9 mmol) was treated with phosphoryl chloride (15 mL) and 3 drops of dry DMF. The mixture was stirred at 80°C for 4 hours, cooled, and evaporated to dryness. The residue was dissolved in dry THF (50 mL) and added, with vigorous stirring, to 880 ammonia (200 mL). After 1 hour, the mixture was diluted with water (200 mL) and extracted with ethyl acetate. The extract was washed with brine, dried (anhydrous magnesium sulfate) and evaporated to give the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 270/272 ($C_{11}H_6ClF_2N_3O$ requires $[M+H]^+$ 270/272).

^1H NMR δ (DMSO-d_6): 7.44 (1H, q), 7.68 (1H, q), 7.75 (1H, t), 8.15 (1H, s), 8.21 (1H, s) and 8.30 (1H, s).

Description 12

3-Chloro-6-(2,3-difluorophenyl)pyridazine-4-carbonitrile

3-Chloro-6-(2,3-difluorophenyl)pyridazine-4-carboxamide (3.03 g, 11.2 mmol) was stirred in phosphoryl chloride (30 mL) at reflux for 3 hours, cooled, and evaporated to dryness. The residue was dissolved in dichloromethane, washed with saturated sodium hydrogen carbonate solution, dried (anhydrous magnesium sulfate) and evaporated to give the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 252/254 ($C_{11}H_4ClF_2N_3$ requires $[M+H]^+$ 252/254).

^1H NMR δ ($CDCl_3$): 7.33 (1H, m), 7.41 (1H, m), 7.97 (1H, t) and 8.23 (1H, s).

Description 13

5-(2,3-Difluorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-ylamine

3-Chloro-6-(2,3-difluorophenyl)pyridazine-4-carbonitrile (2.82 g, 11.2 mmol) and hydrazine hydrate (1.25 mL, 25.8 mmol) were stirred at reflux in ethanol (50 mL) for 1 hour. The mixture was cooled and evaporated to dryness. The residue was triturated with water, and the solid was filtered off and dried, giving the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 248 ($C_{11}H_7F_2N_5$ requires $[M+H]^+$ 248).

^1H NMR δ (DMSO-d_6): 6.10 (2H, s), 7.39 (1H, q), 7.54 (1H, q), 7.82 (1H, t), 8.46 (1H, s) and 12.88 (1H, s).

Synthetic Method N

Example 31

(4-Chlorobenzyl)-[5-(2,3-difluoro-phenyl)-1-*H*-pyrazolo[3,4-*c*]pyridazin-3-yl]-amine

n-Butanol (8 mL) and molecular sieves (4A, 100 mg) were added to 5-(2,3-difluorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-ylamine (265 mg, 1.07 mmol) and 4-chlorobenzaldehyde (451 mg, 3.21 mmol) and the mixture heated at reflux for 24 hours. After cooling to room temperature the solvent was removed *in vacuo*, and anhydrous tetrahydrofuran (8 mL) added. To this solution was added sodium borohydride (91 mg, 2.39 mMol) and the mixture heated at 50°C for 16 hours. The mixture was then filtered and concentrated, then redissolved in methanol (25 mL) and filtered again. The filtrate was again concentrated and dichloromethane (25 mL) added. The sample was filtered again, and the solid obtained redissolved in methanol (5 mL) and purified by preparative HPLC (C18 column, gradient of 10-90% acetonitrile (containing 0.01%trifluoroacetic acid) in water (containing 0.1% trifluoroacetic acid)). The compound was futher purified by running through an SCX cartridge in methanol and product eluted with 2N methanolic ammonia solution. After removal of volatiles and further purification by silica gel chromatography (with 2% methanol in dichloromethane as eluent) the title compound was obtained a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 372/374 ($C_{18}H_{12}F_2N_5Cl$ requires $[M+H]^+$ at m/z 372/374.

^1H NMR δ (DMSO-d_6): 4.51 (2H, d), 7.40 (6H, m), 7.54 (1H, m), 7.83 (1H, m), 8.52 (1H, finely coupled d) 12.95 (1H, s).

Synthetic Method O

Example 28

Cyclopentylmethyl-(5-(2,3-difluorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl)amine

Lithium aluminium hydride (2 mL of a 1M solution in tetrahydrofuran) was added dropwise to a stirred solution of cyclopentanecarboxylic acid 5-(2,3-difluorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl-amide (200 mg, 0.58 mmol) in dry tetrahydrofuran (20 mL) at room temperature. After 24 hours the reaction mixture was quenched with 80 µl of water, 80 µl of sodium hydroxide (40% aq solution) and finally 240 µL of water. The

mixture was filtered and concentrated in vacuo. Purification by column chromatography (dichloromethane to 2% methanol/dichloromethane) afforded the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 330 ($C_{17}H_{17}F_2N_5$ requires $[M+H]^+$ at m/z 330).

^1H NMR δ ($CDCl_3$): 1.0-2.0 (8H, m), 2.3 (1H, m), 3.4 (2H, dd), 4.3 (1H, t), 7.2 (2H, m), 8.0 (1H, m), 8.2 (1H, s), 9.8 (1H, s).

The starting material for Example 28 may be prepared by Description 14

Description 14

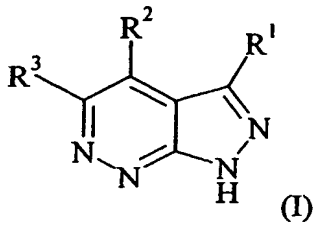
Cyclopentanecarboxylic acid (5-(2,3-difluorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl)-amide

Cyclopentane carbonyl chloride (0.2 mL, 1.38 mmol) was added to a stirred solution of 5-(2,3-difluorophenyl)-1H-pyrazolo[3,4-c]pyridazin-3-ylamine (497 mg, 2.0 mmol) in pyridine (20 mL). The reaction mixture was stirred at 140 °C for 2 h then concentrated in vacuo. Trituration with methanol afforded the title compound as a solid.

^1H NMR δ (DMSO-d_6): 1.5-2.0 (8H, m), 3.0 (1H, dd), 7.4 (1H, m), 7.6 (1H, m), 7.8 (1H, m), 8.8 (1H, s), 11.0 (1H, s), 14.2 (1H, s).

The further Examples described herein were prepared by analogy with Synthetic Methods A-O described above.

Table 1



(I)

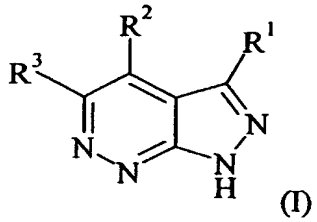
Ex	Method	R^1	R^2	R^3	Calculated Mass	Observed [M+H]+ or [M-H]- or M-
1	A	NHCH2Ph	H	2-Cl-Ph	335.8	336/338
2	B	NHCH2cyclo-pentyl	H	Ph	293.37	294
3	C	NH(3-pyridyl)	H	Ph	288.31	289
4	D	Ph	H	Cl	230.657	231/233
5	E	H	H	3-Pyridyl	197.2	198
6	F	N=CHPh	H	2-Cl-Ph	333.781	334/336
7	G	Ph	H	Ph	272.31	273
8	H	Br	H	Ph	275.108	275/277
9	I	Me	H	Ph	210.239	211
10	H	Br	H	2,3-diF-Ph	311.089	311/313
11	G	3-(2-MeO-pyridyl)	H	Ph	303.324	304
12	J	3-(2-pyridone)	H	Ph	289.297	290
13	K	CH2OCH2Ph	H	Ph	316.362	317
14	L	CH2OH	H	Ph	226.238	227
15	E	H	Me	3-Pyridyl	211.227	212
16	E	H	Ph	Ph	272.31	273
17	M	NH(CH2)2Ph	H	2,3-diF-Ph	351.359	352
18	B	NH(CH2)4(4-Et-Piperazinyl-1-yl)	H	3-Me-Ph	393.536	394
19	M	NHPropyl	H	2,3-diF-Ph	289.288	290
20	N	NHCH2-4-Cl-Ph	H	2,3-diF-Ph	371.777	372/374
21	O	NHCH2cyclo-pentyl	H	2,3-diF-Ph	329.352	330
22	N	NHCH2-3-Cl-Ph	H	2,3-diF-Ph	371.777	372/374
23	N	NHCH2-2-Cl-Ph	H	2,3-diF-Ph	371.777	372/374
24	B	NH(CH2)2Ph	H	3-Me-Ph	329.405	330
25	B	NH(CH2)2OPh	H	3-Me-Ph	345.404	346
26	M	NHHexyl	H	2,3-diF-Ph	331.368	332
27	M	NH(CH2)3Ph	H	2,3-diF-Ph	365.385	366

28	M	NHcyclo-pentyl	H	2,3-diF-Ph	315.326	316
29	M	NHcyclo-hexyl	H	2,3-diF-Ph	329.352	330
30	N	NHCH2-(3-Pyridyl)	H	2,3-diF-Ph	338.32	[M]- 338
31	M	NHCH2-cyclo-propyl	H	2,3-diF-Ph	301.299	302
32	N	NHCH2-(3-Br-Ph)	H	2,3-diF-Ph	416.228	416/418
33	M	NHcyclo-heptyl	H	2,3-diF-Ph	343.379	344
34	M	NH-4-tetrahydrothiapyranyl	H	2,3-diF-Ph	347.392	348
35	M	NH-4-(cyclo-hexyl-CO2Et)	H	2,3-diF-Ph	401.415	402
36	M	NH-(4-methyl-cyclo-hexyl)	H	2,3-diF-Ph	343.379	344
37	M	NH-(4-phenyl-cyclo-hexyl)	H	2,3-diF-Ph	405.45	406
38	M	NH-iso-butyl	H	2,3-diF-Ph	303.315	304
39	M	NH-(2,2-dimethylpropyl)	H	2,3-diF-Ph	317.341	318
40	M	NH-iso-propyl	H	2,3-diF-Ph	289.288	290
41	M	NH-4-(1-propyl-piperidyl)	H	2,3-diF-Ph	372.421	373
42	M	NH-4-(1-methyl-piperidyl)	H	2,3-diF-Ph	344.367	[M]- 344
43	M	NH-4-tetrahydropyranyl	H	2,3-diF-Ph	331.324	332
44	N	NHCH2-(4-MeO-Ph)	H	2,3-diF-Ph	367.358	368
45	N	NHCH2-(4-Br-Ph)	H	2,3-diF-Ph	416.228	416/418
46	M	NH-(2-indanyl)	H	2,3-diF-Ph	363.37	364
47	N	NHCH2(4-(4-Me-piperazin-1-yl)-Ph)	H	2,3-diF-Ph	435.48	434
48	M	NH-cyclo-pentyl	H	3-Pyridyl	280.333	281
49	N	NHCH2-(2-F-Ph)	H	2,3-diF-Ph	355.322	356
50	N	NHCH2-(3-F-Ph)	H	2,3-diF-Ph	355.322	356

5

Claims

1. A compound of formula (I) or a salt thereof and/or a solvate thereof,



(I)

wherein,

R^1 is H, halo, alkyl, hydroxyalkyl, aryl wherein the aryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, $-CF_3$, -OH, $-OCF_3$, $-NO_2$, alkyl, alkenyl, alkynyl, alkoxy and dialkylamino; arylalkoxyalkyl, $-NHR^4$, $-NH(CH_2)_nR^5$, $-N=CHR^6$ or heteroaryl wherein the heteroaryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, $-CF_3$, -OH, =O, $-OCF_3$, $-NO_2$, alkyl, alkenyl, alkynyl, alkoxy and di-alkylamino.

R^2 is H, alkyl or aryl wherein the aryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, $-CF_3$, -OH, $-OCF_3$, $-NO_2$, alkyl, alkenyl, alkynyl, alkoxy and dialkylamino;

R^3 is halo, aryl wherein the aryl group may be optionally substituted with one or more groups, which may be the same or different, selected from halo, -CN, $-CF_3$, -OH, $-OCF_3$, $-NO_2$, alkyl, alkenyl, alkynyl, alkoxy, dialkylamino; or heteroaryl wherein the heteroaryl group may be optionally substituted with one or more groups, which may be the same or different, selected from halo, -CN, $-CF_3$, -OH, $-OCF_3$, $-NO_2$, alkyl, alkenyl, alkynyl, alkoxy, dialkylamino;

R^4 is alkyl, heteroaryl wherein the heteroaryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, -CF_3, -OH, –OCF_3, -NO_2, alkyl, alkenyl, alkynyl, alkoxy and dialkylamino; cycloC_{3-8} alkyl wherein the cycloalkyl group may be optionally substituted with one or more substituents, which may be the same or different, selected from alkyl, aryl and –CO_2R^7, or, said cycloalkyl group is fused with an aryl ring to form a bicyclic moiety; or heterocyclyl wherein the heterocyclyl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, -CF_3, -OH, –OCF_3, -NO_2, alkyl, alkenyl, alkynyl, alkoxy and dialkylamino;

R^5 is cycloC_{3-8} alkyl, aryloxy, aryl wherein the aryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, -CF_3, -OH, –OCF_3, -NO_2, alkyl, alkenyl, alkynyl, alkoxy, dialkylamino; or heteroaryl wherein the heteroaryl group may be optionally substituted with one or more substituents, which may be the same or different, selected from halo, -CN, -CF_3, -OH, –OCF_3, -NO_2, alkyl, alkenyl, alkynyl, alkoxy, dialkylamino;

R^6 is aryl;

R^7 is alkyl; and

n is 1, 2, 3, 4, 5 or 6;

with the proviso that said compound of formula (I) is not selected from the following compounds:

4,5-Diphenyl-3-methyl-1H-pyrazolo[3,4-c]pyridazine;

3, 4,5-Diphenyl-3-methyl-1H-pyrazolo[3,4-c]pyridazine;

3,4,5-Triphenyl-3-methyl-1H-pyrazolo[3,4-c]pyridazine;

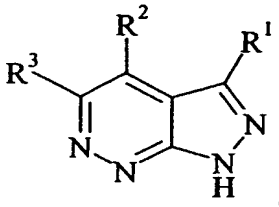
3-(4-Methoxyphenyl)-5-(4-methylphenyl)-1H-pyrazolo[3,4-c]pyridazine;

3-Phenyl-5-(4-methylphenyl)-1H-pyrazolo[3,4-c]pyridazine;

3-(3-Chlorophenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;

3-(3-Bromophenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Bromophenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Chlorophenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Methoxyphenyl)-5-phenyl-1H-pyrazolo[3,4-c]pyridazine;
3,5-Diphenyl-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Methoxyphenyl)-5-chloro-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Fluorophenyl)-5-chloro-1H-pyrazolo[3,4-c]pyridazine;
3-(2,5-Dichlorophenyl)-5-chloro-1H-pyrazolo[3,4-c]pyridazine;
3-(4-Methylphenyl)-5-chloro-1H-pyrazolo[3,4-c]pyridazine; and
3-Phenyl-5-chloro-1H-pyrazolo[3,4-c]pyridazine;

2. A compound of formula (I) as claimed in claim 1, of formula (IA), or a salt thereof and/or a solvate thereof,



(IA)

or a salt thereof, or a solvate thereof, wherein,

R^1 is H, halo, alkyl, hydroxyalkyl, aryl; arylalkoxyalkyl, $-NHR^4$, $-NH(CH_2)_nR^5$, $-N=CHR^6$ or heteroaryl wherein the heteroaryl group may be optionally substituted by alkoxy or =O;

R^2 is H, alkyl or aryl;

R^3 is halo, aryl wherein the aryl group may be optionally substituted by one or more groups, which may be the same or different, selected from halo and alkyl; or heteroaryl;

R^4 is alkyl, heteroaryl, cycloC_{3-8} alkyl wherein the cycloalkyl group may be optionally substituted by one or more substituents, which may be the same or different, selected from alkyl, aryl and $-CO_2R^7$, or, said cycloalkyl group is fused with an aryl ring to form a bicyclic moiety; or heterocyclyl wherein the heterocyclyl group may be optionally substituted by alkyl;

R^5 is cycloC_{3-8} alkyl, aryloxy, aryl wherein the aryl group may be optionally substituted by one or more substituents, which may be the same or different, selected from halo, alkoxy and heteroaryl wherein the heteroaryl may be optionally substituted by alkyl;

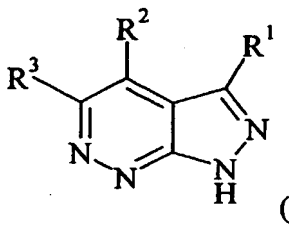
R^6 is aryl;

R^7 is alkyl; and

n is 1, 2, 3 or 4;

with the proviso that said compound of formula (IA) is not selected from the following compounds:
4,5-Diphenyl-3-methyl-1H-pyrazolo[3,4-c]pyridazine;
3,4,5-Triphenyl-3-methyl-1H-pyrazolo[3,4-c]pyridazine;
3-Phenyl-5-(4-methylphenyl)-1H-pyrazolo[3,4-c]pyridazine;
3,5-Diphenyl-1H-pyrazolo[3,4-c]pyridazine; and
3-Phenyl-5-chloro-1H-pyrazolo[3,4-c]pyridazine.

3. A compound of formula (I) as claimed in claim 1, of formula (IB), or a salt thereof and/or a solvate thereof,



(IB)

wherein,

R^1 is H, methyl, phenyl, -N=CHPh, bromo, 3-(2-MeO-pyridyl), 3-(2-pyridone), -CH_2OCH_2Ph, -CH_2OH, -$NH(CH_2)_4$(4-Et-Piperazinyl-1-yl), –$NHCH_2Ph$, -$NH(CH_2)_3Ph$, -NH(3-pyridyl), -$NHCH_2$cyclo-pentyl, -$NHCH_2$cyclo-propyl, -$NH(CH_2)_2Ph$, -NHPr, -$NHCH_2$-(2-Cl-Ph), -$NHCH_2$-(3-Cl-Ph), -$NHCH_2$-(4-Cl-Ph), -$NHCH_2$-(3-Br-Ph), -$NHCH_2$-(2-F-Ph), -$NHCH_2$-(3-F-Ph), -$NH(CH_2)_2OPh$, -$NH(CH_2)_5CH_3$, -NHcyclo-pentyl, -NHcyclo-hexyl, -NHcyclo-heptyl, -$NHCH_2$-(3-pyridyl), -NH-4-tetrahydrothiapyranyl, -NH-4-(cyclo-hexyl-CO_2Et), -NH-(4-methyl-cyclo-hexyl), -NH-(4-phenyl-cyclo-hexyl), -NH-*iso*-butyl, -NH-*iso*-propyl, -NH-(2,2-dimethylpropyl), -NH-4-(1-propyl-piperidyl), -NH-4-(1-methyl-piperidyl), -NH-4-tetrahydropyranyl, -$NHCH_2$-(4-MeO-Ph), -$NHCH_2$-(4-Br-Ph), -NH-(2-indanyl), or -$NHCH_2$(4-(4-Me-piperazin-1-yl)-Ph).

R^2 is H, methyl, or phenyl.

R^3 is chloro, phenyl, 3-methylphenyl, 2-chlorophenyl, 2,3-di-fluorophenyl or 3-pyridyl;

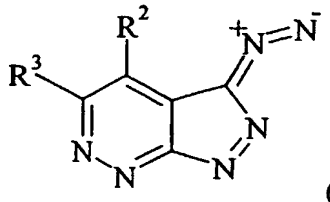
with the proviso that said compound of formula (IB) is not selected from the following compounds:

3,5-Diphenyl-1H-pyrazolo[3,4-c]pyridazine; and

3-Phenyl-5-chloro-1H-pyrazolo[3,4-c]pyridazine.

4. A compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, as claimed in claim 1, substantially as hereinbefore described with reference to any one of the Examples.

5. A process for the preparation of a compound of formula (I) where R^1 is H and wherein R^2 and R^3 are as defined in relation to formula (I), as claimed in claim 1, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II),



(II)

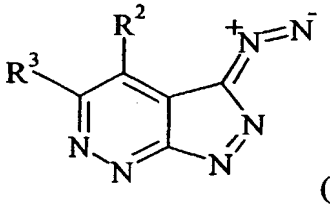
wherein R^2 and R^3 are as defined in relation to formula (I), with a suitable protic solvent and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed.

6. A process for the preparation of a compound of formula (I) where R^1 is halo and wherein R^2 and R^3 are as hereinbefore defined in relation to formula (I), as claimed in claim 1, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II),



(II)

wherein R^2 and R^3 are as defined in relation to formula (I), with an acid and thereafter, if required, carrying out one or more of the following optional steps:

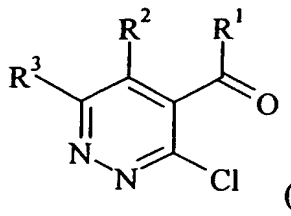
(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed.

7. A process for the preparation of a compound of formula (I) where R^1 is alkyl, hydroxyalkyl, aryl, arylalkoxyalkyl or heteroaryl wherein the heteroaryl group may be optionally substituted by alkoxy or =O and wherein R^2 and R^3 are as hereinbefore

defined in realtion to formula (I), as claimed in claim 1, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (III),



(III)

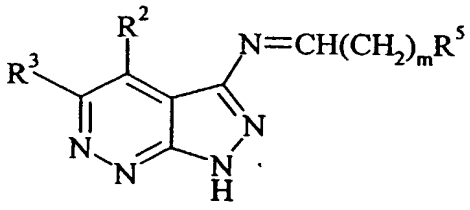
wherein R^1, R^2 and R^3 are as defined in relation to formula (I), with hydrazine or a hydrate thereof and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed.

8. A process for the preparation of a compound of formula (I) where R^1 is – $NH(CH_2)_nR^5$, and wherein R^2, R^3 and R^5 are as hereinbefore defined in relation to formula (I), as claimed in claim 1, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (IV),



(IV)

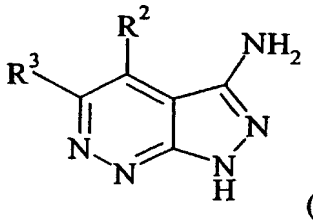
wherein R^2, R^3 and R^5 are as defined in relation to formula (I), and m is n-1, with a reducing agent and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed.

9. A process for the preparation of a compound of formula (I) where R^1 is – $NH(CH_2)_nR^5$, and wherein R^2, R^3 and R^5 are as hereinbefore defined in relation to fomula (I) and n is 1, as claimed in claim 1, or a salt thereof and/or a solvate thereof, which process comprisies reacting a compound of formula (V),



(V)

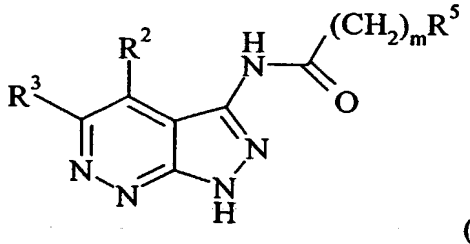
wherein R^2 and R^3 are as defined in relation to formula (I), with an aldehyde, R^5CHO, wherein R^5 is defined in relation to formula (I), and a reducing agent and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed.

10. A process for the preparation of a compound of formula (I) where R^1 is – $NH(CH_2)_nR^5$ and wherein R^2, R^3, R^5 and n are as hereinbefore defined in relation to formula (I), as claimed in claim 1, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (VI),



(VI)

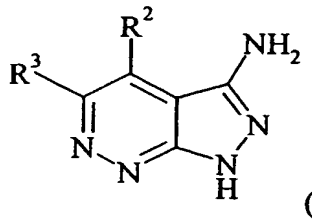
wherein R^2 and R^3 are as defined in relation to formula (I) and m is n-1, and a reducing agent and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed.

11. A process for the preparation of a compound of formula (I) where R^1 is $-NHR^4$ where R^4 is $-CHR^8R^9$, wherein R^8 and R^9 are independently alkyl, or, R^8 and R^9 together with the carbon atom to which they are attached may form an optionally substituted cyclic group which may be fused to an aryl ring to form a bicyclic moiety, and wherein R^2 and R^3 are as hereinbefore defined in relation to formula (I), as claimed in claim 1, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (V),



(V)

wherein R^2 and R^3 are as defined in relation to formula (I), with

(a) a ketone, $R^8R^9C=O$ wherein R^8 and R^9 are independently alkyl, or, R^8 and R^9 together with the carbon atom to which they are attached may form a cyclic group; and

(b) a reducing agent and thereafter, if required, carrying out one or more of the following optional steps:

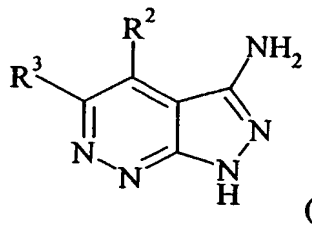
(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed.

12. A process for the preparation of a compound of formula (I) where R^1 is $-NHR^4$ where R^4 is $-CHR^8R^9$, wherein R^8 and R^9 are independently alkyl, or, R^8 and R^9 together with the carbon atom to which they are attached may form an optionally substituted cyclic group which may be fused to an aryl ring to form a bicyclic moiety, and wherein R^2 and R^3 are as hereinbefore defined in relation to formula (I), as

claimed in claim 1, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (V),



(V)

wherein R^2 and R^3 are as defined in relation to formula (I), with

(a) a ketone, $R^8R^9C=O$ wherein R^8 and R^9 are independently alkyl, or, R^8 and R^9 together with the carbon atom to which they are attached may form a cyclic group; and

(b) a reducing agent and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate salt or solvate of the compound so formed.

13. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, as an inhibitor of glycogen synthase kinase-3.

14. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, for the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding

(for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

15. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03171

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
PAJ, EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HOEFLICH K P ET AL: "REQUIREMENT FOR GLYCOGEN SYNTHASE KINASE-3BETA IN CELL SURVIVAL ANDNF-KAPPAB ACTIVATION" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 406, 6 July 2000 (2000-07-06), pages 86-90, XP000986064 ISSN: 0028-0836 cited in the application the whole document	1-15
A	WO 00 26211 A (MORRISSETTE MATTHEW M ;NANTERMENT PHILIPPE G (US); NAYLOR OLSEN AD) 11 May 2000 (2000-05-11) cited in the application page 1, line 24 -page 1, line 31; claims	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 June 2003	11/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03171

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0026211 A	11-05-2000	AU 747776 B2	23-05-2002
		AU 1599700 A	22-05-2000
		CA 2348734 A1	11-05-2000
		EP 1124822 A1	22-08-2001
		JP 2002528543 T	03-09-2002
		WO 0026211 A1	11-05-2000

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/03171

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.